

Drospirenone-Containing Combination Oral Contraceptives Briefing Document

**Joint Meeting of the Reproductive Health Drugs Advisory Committee and the
Drug Safety and Risk Management Advisory Committee**

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Table of Contents

Table of Contents	2
List of Tables	4
List of Figures	6
List of Abbreviations and Definition of Terms	7
1. Executive summary	9
2. Introduction	20
3. Regulatory history	22
3.1 Yasmin.....	22
3.1.1 Postmarketing commitment studies (US and EU).....	22
3.2 YAZ.....	23
3.2.1 Postmarketing commitment study (US and EU)	23
3.2.2 Labeling History Relative to the Risk of VTE with COCs	23
4. Relevant observational studies	27
4.1 Background information.....	27
4.1.1 Venous thromboembolic event.....	27
4.2 VTE risk factors to be considered in the clinical setting.....	28
4.3 Biases to be considered in observational studies comparing the risk of VTE ...	30
4.3.1 Duration of use/Pattern of use	31
4.3.2 Attrition of susceptibles / Healthy user effect	32
4.3.3 Prescription bias (Channeling)	33
4.3.4 Validity of diagnosis for VTE	33
4.3.5 Referral bias / Diagnostic bias.....	34
4.3.6 Conclusion.....	35
4.4 Specific issues relating to the risk of VTE with DRSP-containing COCs.....	35
4.4.1 Mechanism of action – biological plausibility	35
4.5 Information from clinical trials in the development program	36
4.6 Information obtained through the global pharmacovigilance program.....	37
4.7 Observational studies on the risk of VTE with Yasmin.....	37
4.7.1 Observational studies	39
4.7.1.1 Ingenix Yasmin study (Seeger et al., 2007)	39
4.7.1.2 European Active Surveillance (EURAS) OC Study (Dinger et al., 2007).....	43
4.7.1.2.1 Data on VTE.....	43
4.7.1.2.2 Data on ATE.....	46
4.7.1.2.3 Overall conclusions on EURAS	49
4.7.1.3 Long-term Active Surveillance Study (LASS) (Dinger et al., unpublished)	50
4.7.1.3.1 Data on VTE.....	50
4.7.1.3.2 Data on ATE.....	54
4.7.1.4 MEGA study (VanHylckama Vlieg A et al. 2009)	57
4.7.1.5 Danish study (Lidegaard et al. 2009)	60
4.7.1.6 Lidegaard reanalysis (Lidegaard et al., 2011a; Lidegaard et al., 2011b).....	64

4.7.1.7	German case-control study (Dinger et al., 2010)	76
4.7.1.8	PharMetrics study (Jick and Hernandez, 2011).....	79
4.7.1.9	GPRD study (Parkin et al., 2011).....	84
4.7.1.10	FDA-funded study.....	87
4.7.1.10.1	Data on VTE.....	88
4.7.1.10.2	Data on ATE.....	91
4.7.1.11	Additional considerations.....	97
4.7.1.11.1	Selection of an appropriate comparator.....	97
4.7.2	Overall conclusions about the risk of VTE with Yasmin.....	99
4.8	Studies on the risk of VTE with YAZ.....	99
4.8.1	Prospective studies	99
4.8.1.1	INAS-OC (unpublished).....	101
5.	Mechanism of action - chemistry and preclinical data.....	104
6.	Yasmin / Safyral (generics: Ocella)	106
6.1	Clinical development.....	106
6.1.1	Clinical pharmacology	106
6.1.2	Efficacy in clinical trials.....	107
6.1.2.1	Efficacy results – contraception	107
6.1.2.1.1	Overview	107
6.1.2.1.2	Results of contraceptive efficacy	109
6.1.3	Postmarketing efficacy studies.....	109
6.1.3.1	INAS efficacy data	109
6.1.4	Safety in clinical trials.....	111
6.1.4.1	Results	113
6.1.4.1.1	Study population for the safety assessment.....	113
6.1.4.1.2	Medically relevant adverse events with respect to Yasmin	113
6.1.4.1.3	Clinical laboratory evaluations.....	114
6.1.4.2	Safety conclusion in clinical trials.....	114
6.1.5	Benefit-risk profile of Yasmin	114
7.	YAZ / Beyaz (generics: Gianvi).....	116
7.1	Clinical development.....	117
7.1.1	Clinical pharmacology	117
7.1.2	Efficacy in clinical trials.....	117
7.1.2.1	Clinical efficacy – oral contraception	117
7.1.2.2	Clinical efficacy – PMDD.....	118
7.1.2.2.1	Further confirmatory data in literature	120
7.1.2.3	Clinical efficacy – acne vulgaris	121
7.1.2.3.1	Further confirmatory data in literature	122
7.1.3	Postmarketing efficacy studies.....	122
7.1.3.1	INAS efficacy data	122
7.1.4	Safety in clinical trials.....	125
7.1.4.1	Results – oral contraception	127
7.1.4.1.1	Study population for the safety assessment.....	127
7.1.4.1.2	Medically relevant adverse events with respect to oral contraceptives.....	127
7.1.4.1.3	Clinical laboratory evaluations.....	127
7.1.4.2	Results of secondary indications	128

7.1.4.2.1	PMDD	128
7.1.4.2.2	Acne vulgaris.....	128
7.1.4.3	Results – Beyaz	128
7.1.4.4	Safety conclusions	128
7.1.5	Postmarketing safety studies	129
7.1.5.1	VTE data.....	129
7.1.5.2	Other publications on VTE risk with YAZ	129
7.1.6	Benefit-risk profile of YAZ.....	129
8.	Conclusions	130
9.	Reference list.....	132
10.	Appendices	
10.1	Appendix 1: Sponsor’s Clinical Expert Statement on 2009 BMJ Publications (Danish Registry study [Lidegaard et al. 2009] and MEGA study [van Hylckama Vlieg et al. 2009])	
10.2	Appendix 2: Sponsor’s Clinical Expert Statement on 2011 BMJ Publications (US PharMetrics study [Jick and Hernandez 2011] and the UK General Practice Research Database study [Parkin et al., 2011])	
10.3	Appendix 3: Approved US labeling	
10.3.1	Yasmin	
10.3.2	Safyral	
10.3.3	YAZ	
10.3.4	Beyaz	

List of Tables

Table 1-1: Components of DRSP-Containing Oral Contraceptives Approved in the US	11
Table 2-1: Components of DRSP-Containing Oral Contraceptives Approved in the US	20
Table 3-1: Updates to the Warnings and Precautions Sections of Prescribing Information.....	25
Table 4-1: Structured Summary of Study Design as Reported by the Authors - Ingenix.....	40
Table 4-2: Structured Summary of Study Design as Reported by the Authors for VTE - EURAS	43
Table 4-3: Structured Summary of Study Design as Reported by the Authors for ATE - EURAS	46
Table 4-4 Adjusted hazard ratios (HR) and confidence limits for ATE and All TE (EURAS study)	48
Table 4-5: Structured Summary of Study Design as Reported by the Investigators for VTE - LASS.....	50
Table 4-6: Structured Summary of Study Design as Reported by the Authors for ATE - LASS.....	54
Table 4-7 Adjusted Hazard Ratios (HR) and Confidence Limits for ATE	55
Table 4-8: Fatal Outcomes: Number and Mortality Rates per Cohort	55
Table 4-9: Structured Summary of Study Design as Reported by the Authors – MEGA Study	57
Table 4-10: Structural Summary of Study Design as Reported by the Authors – Danish Study	60
Table 4-11: Structured Summary of Study Design as Reported by the Authors – Danish Reanalysis.....	65

Table 4-12: From Final Study Report - Table 10 from Analysis 3 Modified by Sponsor to Include Crude RRs (<i>in italics</i>).....	74
Table 4-13: Excerpt from Table 16, Analysis 3; Restricted to Starters and New Users of LNG- and DRSP-Containing OCs; Columns in italics (IR, RRcrude (1), RRcrude (2), RR***) were added by the sponsor	75
Table 4-14: Impact of Different Assumptions on Rate Ratio Calculations – Table 14 from Analysis 3, reanalysis report	76
Table 4-15: Structured Summary of Study Design as Reported by the Authors – German Case Control Study	77
Table 4-16: Structured Summary of Study Design as Reported by the Authors – PharMetrics Study	80
Table 4-17: Criteria Used to Exclude Subjects From Inclusion into “Idiopathic Cases” Category Reported by Jick et al in Studies of LNG-COC	82
Table 4-18: Studies on VTE and Contraceptives – Idiopathic VTE Event Rates for LNG Subjects Only From the PharMetrics Database	83
Table 4-19: Structured Summary of Study Design as Reported by the Authors – GPRD Study	84
Table 4-20: Structured Summary of Study Design as Reported by the Investigators for VTE – FDA-Funded Study	88
Table 4-21: Structured Summary of Study Design as Reported by the Investigators for ATE – FDA Funded Study	91
Table 4-22: Relative Hazard Ratios - Yasmin versus Comparators for Study Endpoints	94
Table 4-23: VTE Rates for LNG-COC Users Across a Number of Studies.....	98
Table 4-24: Structured Summary of Study Design as Reported by the Investigators for VTE - INAS	101
Table 5-1: Pharmacological Profiles of Selected Progestins in Animal Models	104
Table 6-1: Studies Included in the Assessment of Efficacy	108
Table 6-2: Assessment of Contraceptive Efficacy in All Efficacy Studies	109
Table 6-3: Life-Table Estimates of the Rate of Contraceptive Failure After 1, 2, and 3 Years of Oral Contraceptive Use	111
Table 6-4: Overview of Clinical Studies Providing Information on Tolerability and Safety of Yasmin and Yasmin + Metafolin	112
Table 7-1: Summary of Studies Providing Contraceptive Efficacy Data	117
Table 7-2 Clinical Development Program: Overview of Clinical Studies to Evaluate the Efficacy of YAZ in the Treatment of PMDD	119
Table 7-3 Overview of Clinical Phase 3 Studies to Evaluate the Efficacy of YAZ in the Treatment of Moderate Acne Vulgaris	121
Table 7-4: Overview of Clinical Studies to Assess the Tolerability and Safety of YAZ and Beyaz.....	126

List of Figures

Figure 3-1: Drospirenone Containing Oral Contraceptives – US Approvals and Indications.....	22
Figure 3-2: Submission by the Sponsor of the Internal Scientific Analysis of the 2009 and the 2011 BMJ Publications, LASS, and the 2010 and 2011 Labeling Approvals.....	24
Figure 4-1: Combined Oral Contraceptives: Data from the Transnational Study	31
Figure 4-2: Risk Ratios of Combination Oral Contraceptives Containing Specified Progestagens Compared with Levonorgestrel for Women Aged 25-44 Years by Year of Market Introduction	32
Figure 4-3: Timeline of Studies Relative to Their Publication Date and the Time Interval They Encompass	39
Figure 4-4: Detection of Risk of VTE Among DRSP-Containing and LNG-Containing COCs in Lidegaard 2009.....	64
Figure 4-5: Relative Risk of VTE According to Length of Use – Lidegaard BMJ 2009 and 2011	70
Figure 4-6: Age distribution of Yasmin and LNG2 users at Kaiser and Medicaid sites	95
Figure 6-1: Life-Table Estimates of Contraceptive Failure Associated With the Use of 24-Day Regimens of DRSP and EE, 21-Day Regimens of DRSP and EE, and Other Oral Contraceptive Pills	110
Figure 7-1: Life-Table Estimates of Contraceptive Failure Associated With the Use of 24-Day Regimens of DRSP and EE, 21-Day Regimens of DRSP and EE, and Other Oral Contraceptive Pills	124
Figure 7-2: Life-Table Estimates of Contraceptive Failure. Comparison of Two 24-Day and Two 21- Day Regimens of DRSP and EE (triangle) and Norethisterone Acetate an EE (square).....	124

List of Abbreviations and Definition of Terms

List of abbreviations

AMI	acute myocardial infarction
AST	aspartate transaminase
ATE	arterial thromboembolic event/ arterial thromboembolism
AUC	area under the concentration vs. time curve from zero to infinity
AUC(0-24h)	AUC from time 0 to 24 h
BMI	body mass index
BMJ	British Medical Journal
C _{max}	maximum concentration
CHC	combined hormonal contraceptive
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CK	creatinine kinase
CK-MB	creatinine kinase MB fraction
CMA	chlormadinone acetate
COC	combination oral contraceptive
CPA	cypoterone acetate
CT	computed tomography
CVA	cerebrovascular accident
DRSP	drospirenone
DSG	desogestrel
DVT	deep vein thrombosis
E2	17β-estradiol/natural estradiol
ECG	electrocardiogram
EE	ethinyl estradiol
EMA	European Medicines Agency
EU	European Union
EURAS	European Active Surveillance
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GPRD	General Practice Research Database
h	hour
HR	hazard ratio
ICD	International Classification of Diseases
INAS-OC	International Active Surveillance Study of Women taking Oral Contraceptives
IR	incidence rate
IRR	incidence rate ratio
LASS	Long-term Active Surveillance Study for Oral Contraceptives
LDH	lactic dehydrogenase
LH	luteinizing hormone
LNG	levonorgestrel
MEB	Medicines Evaluation Board
MEGA	Multiple Environmental and Genetic Assessments of risk factors for venous thrombosis
MI	myocardial infarction
MRI	magnetic resonance imaging
N	number of subjects
NA.	not available/not applicable
NDA	New Drug Application
NETA	norethindrone acetate
NGM	norgestimate
NOHC	Non-Oral Hormonal Contraceptives
OC	oral contraceptive

OR	Odds Ratio
PE	pulmonary embolism
PET	positron-emission tomography
PhVWP	Pharmacovigilance Working Party
PI	Pearl Index= number of pregnancies per 100 women years
PLR	Physician Labeling Rule
PMDD	premenstrual dysphoric disorder
PMS	premenstrual syndrome
RAAS	renin-angiotensin-aldosterone system
RR	rate ratio or relative risk
SAE	serious adverse event
SHBG	sex hormone binding globulin
SLE	systemic lupus erythematosus
SSRI	selective serotonin reuptake inhibitor
TE	thromboembolism
TIA	transient ischemic attack
UK	United Kingdom
US	United States
V/Q	ventilation-perfusion
VTE	venous thromboembolic event/venous thromboembolism
WY	women years
ZEG	Center for Epidemiology and Health Research, Berlin, Germany

Product names

Yasmin®	Oral contraceptive containing 3 mg drospirenone (DRSP) plus 0.03 mg EE per tablet One tablet daily for 21 days, followed by a 7-day hormone-free interval
Safyral®	Yasmin (containing EE as betadex clathrate) supplemented with Metafolin Days 1 to 21: 3 mg DRSP + 0.03 mg EE + 0.451 mg Metafolin per tablet Days 22 to 28: 0.451 mg Metafolin per tablet One tablet daily for 28 days per treatment cycle.
YAZ®	Oral contraceptive containing 3 mg DRSP plus 0.02 mg EE (as betadex clathrate) per tablet. One tablet daily for 24 days followed by one placebo tablet for 4 days.
Beyaz®	YAZ supplemented with Metafolin Days 1 to 24: 3 mg DRSP + 0.02 mg EE + 0.451 mg Metafolin per tablet Days 25 to 28: 0.451 mg Metafolin per tablet One tablet daily for 28 days per treatment cycle.
Metafolin®	L-5-methyltetrahydrofolate (L-5-methyl-THF) as calcium salt International nonproprietary name: levomefolate calcium
Yasminelle	Oral contraceptive containing 3 mg DRSP plus 0.02 mg EE (as betadex clathrate) per tablet. One tablet daily for 21 days followed by one placebo tablet for 7 days. (Not marketed in the US)
Ocella	Oral contraceptive containing 3 mg drospirenone (DRSP) plus 0.03 mg EE per tablet One tablet daily for 21 days, followed by a 7-day hormone-free interval (Generic equivalent to Yasmin)
Gianvi	Oral contraceptive containing 3 mg DRSP plus 0.02 mg EE (as betadex clathrate) per tablet. One tablet daily for 24 days followed by one placebo tablet for 4 days. (Generic equivalent to YAZ)

Note: throughout this document, the symbol ® indicating a proprietary name is not displayed for the above products. However, the omission of the symbol does not imply that these names are not protected.

1. Executive summary

Yasmin is a combination oral contraceptive (COC) that contains the progestin drospirenone (DRSP) and was first approved in the United States (US) in 2001. Following its approval in the US and in Europe, the sponsor conducted large cohort postmarketing commitment safety studies as agreed with the respective health authorities to assess venous thromboembolic events (VTE), an established risk for all COCs, with Yasmin compared to other COCs. These studies concluded that the risk of VTE with Yasmin was similar to all the COCs studied. Since 2009, other observational studies were published concluding that the risk of VTE with Yasmin is higher than the risk seen with other COCs, specifically levonorgestrel (LNG)-containing COCs (See [Figure 4-3](#)). It is in light of these seemingly discordant results that the US Food and Drug Administration (FDA) has convened this Advisory Committee.

This Executive Summary provides a high level review of the sponsor's perspective on the topic. A more detailed and comprehensive discussion is presented in the main body of the Briefing Document.

DRSP-containing COCs are among the most extensively studied COCs both in clinical development and in postmarketing commitment safety studies. They are clinically differentiated from other COCs based on a variety of factors, including the long half life (30 hours) of DRSP, as well as its antimineralocorticoid and antiandrogenic activities. They have expanded the range of contraceptive options available to women and their health care providers ([Speroff, 2005](#)). The data generated through postmarketing commitment safety studies provide strong evidence that the risk of VTE with DRSP-containing COCs is similar to the other COCs studied, including LNG-containing COCs ([Dinger et al., 2007](#); [Seeger et al., 2007](#)). Studies suggesting an increased risk of VTE with DRSP-containing COCs have serious methodologic limitations, which lead to bias ([Jick and Hernandez, 2011](#); [Lidegaard et al., 2009](#); [Lidegaard et al., 2011b](#); [Parkin et al., 2011](#); [van Hylckama Vlieg et al., 2009](#)). In all, the current body of rigorous scientific evidence strongly supports a favorable benefit-risk profile for DRSP-containing COCs when used in accordance to labeling.

For the purpose of introduction, a VTE can be a serious medical condition that requires immediate medical attention. The two most common presentations for VTE are deep vein thrombosis (DVT) in the lower extremities and pulmonary embolism (PE), a clot that floats off to lodge in a blood vessel in the lungs. Almost two-thirds of VTE cases present as a DVT, about one quarter as PE, and a small group of patients present with both DVT and PE. VTE is a well-recognized rare complication associated with the use of COCs as a drug class; this is a class effect of estrogen. As stated in the most recent labels (physicians labeling rule [PLR] format) across current COCs, the expected frequency for VTE in women using COCs is in the range of 3-9/10,000 women years (WY), with the risk being highest during the first year of use. These labels also note that pregnancy increases the risk of VTE as much or more than the use of COCs.

Contraindications as well as warnings and precautions relative to risk factors for VTE are outlined in the US label (eg, Yasmin US package insert). Across all COC labels, a box warning discusses the relationship between cigarette smoking and serious cardiovascular events; COC use is contraindicated in women who smoke and are over age 35. The current labels for COCs, as a class, clearly indicate that COCs should not be prescribed to women at a high risk of arterial and venous thrombotic diseases who are known to: smoke (if over age 35), have a DVT or PE, now or in the past, have cerebrovascular disease, coronary artery disease, uncontrolled hypertension or thrombogenic valvular or thrombogenic rhythm disease of the heart (eg, subacute bacterial endocarditis with valvular disease, or atrial fibrillation), have inherited or acquired hypercoagulopathies, have diabetes mellitus with vascular disease or have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35. The Warnings and Precautions section of COC class labeling further elaborates on the risk of thromboembolic disorders and other vascular events. The label clearly states that the use of COCs is associated with increased risk of VTE, as well as arterial thromboembolism (ATE), especially in women with other risk factors for these events.

COCs consist of both an estrogen and a progestin component and prevent ovulation by inhibiting gonadotropin secretion via an effect on both hypothalamic and pituitary centers. The estrogen component suppresses follicle-stimulating hormone (FSH) secretion, thus preventing the selection and emergence of a dominant follicle. The progestin component primarily suppresses luteinizing hormone (LH) secretion, thus preventing ovulation, and is widely acknowledged as the primary driver of contraceptive efficacy ([Schreiber CA, 2009](#)). COCs have been approved in the US since 1960.

Up to the time of the clinical introduction of Yasmin, the progestin component of all COCs in the US was derived from 19-nortestosterone, including the progestin LNG. In contrast, DRSP is a derivative of spironolactone. DRSP differs from other progestins in that it displays antimineralocorticoid activity, similar to naturally occurring progesterone. In addition, DRSP displays antiandrogenic effects.

There are a number of DRSP-containing COCs approved in the US. Yasmin is a 21-day active/7 day placebo COC preparation that was approved in the US in 2001 to “prevent pregnancy.” YAZ is a 24-day active/4 day placebo COC preparation that was approved in the US in 2006 to “prevent pregnancy and to treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception.” YAZ was subsequently approved in 2007 to “treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control.” Safyral, approved in the US in 2010, and Beyaz, approved in the US in 2010 are the respective folate-containing preparations of Yasmin and YAZ, and each carry the additional indication to “raise folate levels in women who choose to use an oral contraceptive for contraception.”

Table 1-1: Components of DRSP-Containing Oral Contraceptives Approved in the US

	DRSP	EE	Hormone Treatment Days	Hormone Free Days	Levomefolate Calcium	Summary of Indication(s)
Yasmin (+generics)	3 mg	0.03 mg	21	7	No	Contraception
Safyral	3 mg	0.03 mg	21	7	0.451 mg	Contraception + Raise folate levels
YAZ (+generics)	3 mg	0.02 mg	24	4	No	1. Contraception 2. (1)+ PMDD 3. (1)+ Acne
Beyaz	3 mg	0.02 mg	24	4	0.451 mg	1. Contraception 2. (1)+ PMDD 3. (1)+ Acne 4. (1) + Raise folate levels

DRSP = drospirenone, EE = ethinyl estradiol, PMDD = premenstrual dysphoric disorder

DRSP-containing COCs have been extensively studied in preclinical and clinical programs. There was a total of 7508 women exposed to DRSP-containing COCs for the new drug applications (NDAs) for Yasmin, Safyral, YAZ, and Beyaz. This represents one of the most extensive clinical development programs in the COC class. In these clinical studies, a total of 3 cases of VTE and 1 case of suspected thrombosis in the leg were reported. No safety signal of an increased risk of VTE among study participants was detected.

Since the 1980s, attention has focused on the association between COCs and the risk of VTE. The original focus was on the estrogen component. It has long been known that elevated levels of systemic estrogens (both endogenous and exogenous) are associated with an increased risk of VTE; eg, the high physiological levels of estrogens, such as those seen during pregnancy, are associated with a marked increased risk for VTE. Pregnancy and the post-partum period confers among the highest attributable risk for VTE in women of reproductive age, with estimates of a 5-10 fold increase over the non-pregnant state in otherwise healthy individuals.

Ethinyl estradiol (EE) is the most common estrogen in COCs and has been historically linked to the increased risk of VTE in COC users. Early COCs contained 0.05 mg or more of EE. With time, COCs with doses of EE below 0.05 mg were introduced, now ranging from 0.035 mg down to 0.01 mg, and referred to as “low-dose” COCs. With time, it was demonstrated that lower doses of EE were associated with a lower risk of VTE. All DRSP-containing COCs are in the “low-dose” COC category.

Since VTE is a rare event, a clinical development program for COCs cannot provide an accurate estimate of frequency for VTEs. In addition, postmarketing adverse event (AE)

data from spontaneous sources (‘spontaneous reporting’) have well-known limitations. The postmarketing safety data with Yasmin and YAZ from spontaneous reporting are consistent with the known safety profile of COC products as a class. Based on the available data, no new and/or unexpected safety signal could be identified and the sponsor’s assessment of the benefit-risk balance is favorable.

Accordingly, well-designed, postmarketing observational studies can enhance knowledge about VTE risks with COCs following product approval.

In the mid 1990s, observational studies not only assessed the potential contribution of lower doses of EE, but also sought to compare the progestin component of COCs with respect to the risk of VTE. The scientific debate on this topic is still ongoing, however, in addition to general principles of sound study design, a number of key scientific and methodological principles have been established for the design and conduct of observational studies and are applicable to the study of the VTE risk when comparing different COCs. These include accounting for the following sources of potential bias (see [Section 4.3](#) for full descriptions):

1. **Duration of use / Pattern of use:** The risk of VTE is highest during the first year of use of COCs. The specific pattern of use (ie, repeat, intermittent use, switching or first ever use) also influences the risk of VTE with an increase upon resuming COC use. It is thus essential to appropriately account for duration and pattern of use when comparing COCs.
2. **Attrition of susceptibles / Healthy user effect:** First time ever users of COCs, as a group, include more at-risk individuals for VTE, because this group includes women with an as yet undetected predisposition to VTE. Conversely, women who have previously used COCs and continued their use are a group at lower risk for VTE, other things being equal, because individuals at an increased risk of VTE have already been identified from prior use, and many may no longer be candidates for COCs (a winnowing effect). Ideally, well designed observational studies should establish balance of these characteristics and other risk factors for VTE between the treatment groups compared, or these factors should be taken into account in the analysis. It is essential to compare women with similar risk profiles for VTE between the cohorts.
3. **Prescription Bias (channeling):** When a given COC is perceived by clinicians as offering an advantage, a preference to select and recommend that particular COC for women at higher risk may occur. Thus women taking the ostensibly safer pill are at inherently higher risk of complications than are the women taking other pills, which biases any comparison against the safer pill. If the baseline differences in risk factors between treatment groups are not taken into account, results are predictably biased against the COC with the perceived safety advantage.
4. **Validity of diagnosis for VTE:** The diagnosis of VTE must be validated through medical records review. Ideally, the adjudication should be performed by an exposure-blinded individual. Failure to conduct medical record validation may lead to a high rate of false positives. Studies indicate that only 20% of women referred for VTE evaluation ultimately have a diagnosis of VTE (Soehne et al. 2009), and even

those seen in hospital are commonly misdiagnosed (Severinsen 2010). Unless clinical medical record validation is conducted, there may be an amplification of the next effect, referral bias. Systematic over-diagnosis of VTE among women using COCs or a specific brand of COC biases results.

5. **Referral / Diagnostic (Detection) bias:** Given leg complaints, women using COCs are more likely than are other women to seek care and to get diagnostic evaluation (Collet et al., 1994). Moreover, women who use COCs that are new to the marketplace, or COCs that become identified as potentially carrying an increased risk of VTE, are more likely to be referred for an evaluation for VTE.

From the onset, it must be acknowledged that no observational study methodology or design achieves perfection. However, the more key elements relevant to a specific scientific question can be accounted for appropriately, the more likely a study is to produce accurate and reproducible results.

Yasmin was approved in the US and Europe against the backdrop of the rapidly evolving science on the risk of VTE with COCs. The sponsor was aware of the potential for concerns being raised about a COC containing a new progestin (DRSP) entering the marketplace. These concerns were discussed with Regulatory Authorities and the sponsor committed to the European Medicines Agency (EMA) to conduct a prospective large-scale cohort trial in Europe, looking at the risk of VTE for Yasmin compared to other COCs in routine clinical use. The sponsor met this commitment by commissioning the European Active Surveillance Study (EURAS). In the US, interactions with the FDA resulted in the postmarketing commitment to conduct the Ingenix study, another large cohort study, to assess among other outcomes the risk of VTE comparing Yasmin to other low-dose COCs in clinical use in the US.

Both of these cohort studies were designed and conducted by independent investigator groups and commissioned by the sponsor. Each study was designed based on well-established methodological principles for cohort studies. In addition, each study considered and attempted to address some of the potential biases identified above, especially with regard to duration/pattern of use and validity of diagnosis for VTE. The protocols were submitted to and agreed upon with the respective regulatory authorities (Ingenix to FDA, EURAS to EMA). Regular interim and final study reports for each study were submitted to the FDA and regulatory agencies around the world. The primary reports for both studies were published in peer-reviewed journals in 2007. These two studies assessed the risk of VTE, but used different methodological approaches.

The Ingenix study (Seeger et al., 2007) was a cohort study conducted within a US health insurer database (United Healthcare). The data compared Yasmin to all other COCs in use in the population, with no head-to-head comparison to LNG-containing COCs. The Ingenix study was able to accurately track duration and pattern of use. Balance was established and demonstrated between Yasmin and other COC users through propensity score matching. A separate internal validation study suggested that the cohorts were balanced for additional covariates not included in the propensity score estimation. VTE events and sudden deaths were adjudicated on the basis of a review of clinical records performed by exposure-blinded expert clinicians. Comparing the risk of VTE for Yasmin

users to users of other COCs, the authors reported a rate ratio of 0.9 (95% CI 0.5-1.6). Stated alternatively, Yasmin was associated with no increase in VTE risk compared with other COCs.

The EURAS study (Dinger et al., 2007) was a prospective, non-interventional cohort study conducted in Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom (UK). The selection of an individual COC was left up to the woman and her clinician, at which time entry into the study was offered. At study entry the clinician reported relevant information on the health status of the woman. Women were followed from 1.5 to 5 years. During follow up the study relied on patient self-reporting relative to the type of COC used, including duration and pattern of use, as well as for the report of potential VTE cases. All diagnostic procedures were based on local clinical standards, with no standardized criteria across all study sites. The EURAS study was powered to compare Yasmin to LNG-containing COCs as well as to all other oral contraceptives (OCs). Groups were analyzed based specifically on duration of use and pattern of use, as well as on the basis of history of prior use, including a first-time ever use cohort. The adjudication of VTE cases was achieved through a direct review of medical records and adjudication by 3 exposure-blinded experts. Finally, key risk factors were ascertained by questionnaire at baseline and updated every 6 months, with analyses adjusted for risk factors. The authors reported the relative risk of VTE for Yasmin users compared to LNG-COC users at 1.0 (95% CI 0.6-1.8) and compared to users of all OCs in the study at 0.9 (95% CI 0.6-1.4). Again, Yasmin was associated with no increase in risk of VTE compared with other COCs. Of note, the EURAS study is the most rigorously designed prospective cohort study published to-date comparing the risk of VTE between different COCs.

A summary of these study findings was included in a revision of the US package insert in April 2010 for Yasmin. The “... *prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel.*” ... the EURAS study “*showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC).*” (Note: The same wording was also implemented in April 2010 for YAZ, and has been incorporated into the labels for Safyral and Beyaz).

The Ingenix and EURAS studies integrated sound principles for observational studies. The EURAS study accounted for the above mentioned potential biases in comparing the risk of VTE between users of different COCs. The Ingenix study used propensity score matching to achieve balance between the treatment groups compared. Taken together, these post-approval commitment safety studies provide strong and consistent evidence that the risk of VTE for Yasmin is similar to the other COCs studied.

In addition to the Ingenix and EURAS studies, the sponsor initiated and provided support to two additional studies on the risk of VTE with Yasmin. One study is the Long-Term Active Surveillance study (LASS), providing an additional 5-year follow-up for women that were originally enrolled in the EURAS study; the final study report was recently submitted to the FDA and future publications are expected. The other study is a case-

control study conducted in Germany ([Dinger et al., 2010](#)). The results from both of these completed studies provide further evidence that the risk of VTE for Yasmin is similar to the other COCs studied (see Sections 4.7.1.3 and 4.7.1.7, respectively, for full description and commentary).

In August 2009, two studies on the risk of VTE with various COCs were published in the British Medical Journal (BMJ): the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study ([van Hylckama Vlieg et al. 2009](#)) and the Danish Registry study ([Lidegaard et al. 2009](#)). The authors of both studies independently reached conclusions that suggested that the risk of VTE is increased with use of Yasmin when compared to LNG-containing COCs.

The MEGA study ([van Hylckama Vlieg et al., 2009](#)) was a population-based case-control study conducted in the Netherlands, with VTE cases gathered from 6 participating anticoagulation clinics. Assessment of COC use was conducted through a patient-completed questionnaire, with an assessment of duration of use possible for a sub-set of patients and controls. A major shortcoming of the MEGA study was the process to select controls. These were a highly selective group, unlikely to be an appropriate match to the VTE cases. Specifically, 40.5% of the controls were recruited from female partners of males with a history of VTE and followed in the participating anticoagulation clinics, a population unlikely to represent women in The Netherlands. The remainder of controls was recruited from the overall general population of the Netherlands, identified by random-digit dialing, a better approach. The authors, comparing the risk of VTE for Yasmin vs. LNG-COC users, reported an odds ratio of 1.7 (95% CI 0.7-3.9). Underlying these non-statistically significant numbers, the number of cases among Yasmin users was only 1.2% of all VTE cases (19 Yasmin cases out of 1524 total cases). Stated alternatively, Yasmin was not associated with a statistically significant increase in risk of VTE compared to LNG-containing COCs in the MEGA Study.

The Danish study ([Lidegaard et al., 2009](#)) was a cohort study conducted in Denmark, with data linked across 4 national Danish registries. The large number of subjects included in the databases provided access to a large number of VTE cases and potential controls, associated with high statistical power. The database also provided access to filled prescriptions and several potential confounding variables, including age and year of data collection. The authors, however, relied on diagnostic coding within the databases to ascertain VTE cases, with no validation through medical record reviews or adjudication by exposure-blinded clinical experts. Another major source of bias in this study was improper assessment of duration of COC use. While the authors proposed that they appropriately accounted for this key bias, the data suggest otherwise. Contrary to the well-established epidemiology of VTE, LNG-COC users did not show a higher risk of VTE during the first year of use (<1 year). The most likely explanation for this finding is that long-term LNG-COC users were misclassified as first year users. It was therefore not possible for the study investigators to accurately categorize duration of use for LNG-COC users according to the categories designated by the authors themselves (<1 year, 1-4 years and >4 years). Consistent with this view is the observation that when comparing the risk of VTE between Yasmin and LNG-COC users, the overall rate ratio was reported as 1.64 (95% CI 1.27-2.10), whereas restricting analysis to long-term users, no difference in risk was observed when comparing Yasmin and LNG-COC users for the duration of use

period characterized as 1-4 years. Overall, the methodologic limitations of this study, including a lack of clinical validation of VTE cases, and the likely inappropriate characterization of duration of use for the major comparator cohort (LNG-COCs), render the results unreliable.

During an assessment of the Danish study, the EMA requested that Bayer provide funding to Prof. Lidegaard to reanalyze the data while addressing fundamental methodological issues. This initiative will be referred from this point on as the “Danish study reanalysis.” Multiple analyses were performed by the investigators, some of which were reported in October 2011 ([Lidegaard et al., 2011b](#)) while other analyses were included only in the final study report submitted to the EMA, the FDA, and other regulatory agencies.. The publication reports that after adjustment for length of use, users of Yasmin were at least at twice the risk of VTE compared with users of COCs with LNG. More importantly, the 2011 reanalysis of the Danish study provides evidence that the results from the 2009 publication are invalid. The reanalysis now reveals the expected increase in the risk of VTE during the first year of use for LNG-containing COCs; it highlights that at least 25% of cases recorded as VTE in the registries are not confirmed clinically. However, on its own merit, the 2011 reanalysis still suffers from significant methodologic limitations, such as inappropriate allocation for duration and pattern of use and lack of validation for VTE cases that make the results of the reanalysis also invalid.

In April 2011, two additional cohort studies with nested case-control analysis using 2 databases were published in the BMJ: the US PharMetrics study (Jick and Hernandez 2011) and the UK General Practice Research Database (GPRD) study (Parkin et al., 2011). The authors of both of these studies reported only non-fatal idiopathic VTE cases, and compared Yasmin to LNG-COC users. The authors of both studies concluded that the risk of VTE is increased with Yasmin when compared to LNG-containing COCs.

The US PharMetrics database study ([Jick and Hernandez, 2011](#)) used this medical and pharmaceutical claims database typically used to assess the impact or association of a disease condition with healthcare resource utilization and costs in a commercially insured population and to gain an understanding of treatment patterns of pharmaceuticals such as treatment duration and dosage strength. However, the authors of the current study sought to expand the use of the PharMetrics database beyond these primary purposes. It is not clear whether or not the authors accounted for continuous enrollment in the database by members of the study cohort. Access to prescription data allowed selection of cases and controls blinded to type of COC used, as well as matching of cases and controls based on age and index year. The definition of “idiopathic” is highly subjective and severely limits extrapolation of any results to the general population of women. Stated alternatively, to focus on idiopathic cases, the investigators excluded many subjects from the overall pool of women. Because of the authors’ method for excluding “non-idiopathic” cases, it is likely that this approach led to the differential exclusion of cases, with the disproportional exclusion of LNG-COC users. This approach may have compromised the balance between Yasmin and LNG-COC users on measured and unmeasured confounders, giving rise to the potential for a healthy user effect bias among the LNG-COC users. In addition, no validation of medical record review was performed in this study. The authors reported that the rate ratio for “non-fatal idiopathic VTE” was 2.8 (95% CI 2.1-3.8) (age adjusted) when comparing Yasmin to LNG-COC users. This lack of validation contradicts

principles espoused by Jick herself, as well as draft guidance from the FDA for this type of research with administrative databases ([FDA, 2011](#))

The UK GPRD study (Parkin et al 2011) relied on data extracted from the UK GPRD ([Parkin et al., 2011](#)). The GPRD database is a primary healthcare database broadly representative of the UK population. It offers access to the medical records of registered individuals including demographic data, medical diagnoses, consultant and hospital referrals and record of prescriptions issued. This allows access to information on several VTE risk factors and potential confounders: body mass index (BMI), smoking, history of varicose veins, antidepressant use, and current duration of COC use. The possibility to validate VTE diagnosis by requesting copies of medical records from hospitalization and referrals was not fully used. The authors validated fewer than half of all included VTE cases and did this on a consecutive basis (no random sampling approach used). Finding more cases of PE than VTE raises significant concerns about the validity of this approach as this distribution does not reflect clinical reality. In addition, women in the UK who were prescribed Yasmin during the study period were very likely to be different from those prescribed LNG-containing COCs (selection bias). Yasmin was generally under formulary restriction (differential formulary access), in contrast to LNG-containing COCs which had unrestricted access and were generally provided at minimal cost. The authors reported an incidence ratio of 2.7 (95% CI 1.5-4.7) when comparing Yasmin to LNG-COC users for “non-fatal idiopathic VTE.”

On 27 October 2011 the FDA posted to their drug safety communication website the results of an FDA-funded study on “Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints.” This was a retrospective cohort study involving insurance claims and medical record data conducted at two sites from the Kaiser Permanente system (northern and southern California) and two state Medicaid systems (Tennessee, Washington), each associated with an academic institution. With respect to Yasmin, the authors concluded that Yasmin was associated with a significantly higher risk of VTE relative to low-estrogen comparators, including a hazard ratio (adjusted for age, site, year of entry into study) of 1.45 (95%CI 1.15-1.83) compared to LNG-containing COCs. Unfortunately, it appears that this study so far has been limited to extracting data purely from the administrative components of the databases being used, and suffers from many of the same methodological shortcomings as do other large administrative database studies in the field in this area of research. For one, the study lacks internal consistency; while VTE (and ATE) rates are purportedly elevated with Yasmin, the risk of death is significantly lower. When one examines the results, the pattern of risk (incidence rate ratio [IRR]) for VTE over time for Yasmin is erratic and not biologically plausible. The study fails to account for key factors related to VTE, namely obesity, full personal history of VTE, and family history of VTE. There is evidence of significant inequality in baseline characteristics in the Yasmin group versus the comparators, particularly with regard to age distribution. In the case of major imbalances between groups, the application of regression methods (Cox proportional hazard) is unreliable. Based on an initial assessment of this recent report, there appear to be numerous design, methodological, and statistical flaws such that the results of the FDA-sponsored study does not demonstrate a causal relationship between use of Yasmin and elevated rate of VTE.

The sponsor has been carefully studying and monitoring VTE in relation to its products. This has included actively supporting two large post-approval commitment safety studies; both with input from the health authorities. These two prospective cohort studies were designed specifically to account for key elements in the assessment of the risk of VTE when comparing different COCs. Both prospective studies, using different methodologies and women on different continents, have found no increase in risk of VTE for Yasmin compared to other available COC formulations, including LNG-containing COCs. By contrast, the MEGA study (van Hylckama Vlieg et al. 2009), the Danish Registry study (Lidegaard et al. 2009) and its reanalysis ([Lidegaard et al., 2011a](#); [Lidegaard et al., 2011b](#)), the US PharMetrics study (Jick and Hernandez 2011), the UK GPRD study (Parkin et al 2011) and the FDA-funded study ([Ouellet-Hellstrom et al., 2011](#)) suffer from severe methodological limitations that undermine the reliability of the reported conclusions. In the sponsor's opinion, the findings reported in these 5 publications and the recently released FDA-funded study does not change the overall assessment about the safety of DRSP-containing COCs. The sponsor reaffirms that the overall body of available scientific evidence continues to support that the risk of developing VTE in women using DRSP-containing COCs is comparable to other combination birth control pills studied, including those containing LNG when used in accordance with the label.

All of the studies discussed to this point have focused on Yasmin only. YAZ differs from other COCs, including Yasmin, in its formulation (lower dose of EE), regimen (24 days vs. 21 days), and range of indications (contraception, contraception+PMDD, contraception+acne). Nonetheless, the sponsor was aware that concerns around the risk of VTE with YAZ may arise, based on the history of such concerns with newly-introduced COCs.

The successful completion of the EURAS trial in 2005 demonstrated that such a large prospective cohort study could be conducted according to protocol. There was a convergence of opinion between the FDA, the EMA, and the sponsor that an active surveillance study modeled after the EURAS study would be the desirable approach to a post-approval study commitment for YAZ. The protocol was completed in concert with both the FDA and the EMA and is referred to as the International Active Surveillance Study (INAS-OC).

The INAS study started recruitment in the US upon the approval of YAZ in 2006 and was expanded to Europe when YAZ was approved there. Recruitment has been completed and includes a total of 52,218 US and 33,042 European study subjects. The study follows the design of the EURAS study. The study is performing equally well in the US as in Europe with regard to questionnaire completion, study subject retention, and access to medical records for VTE case validation. Interim results are regularly shared on schedule with the FDA, the EMA, and other regulatory authorities. The available results from the latest interim analysis indicate that the risk of VTE for YAZ is similar to other OCs or LNG-containing COCs.

In summary, DRSP-containing COCs were developed through some of the most extensive clinical development programs in the field of oral contraception. They are clinically differentiated from other COCs and expand the range of options available to women and their clinicians. The sponsor carried out its postmarketing commitment safety studies in

agreement with the FDA and the EMA. These completed studies, which incorporate the best methodological principles of observational research to assess the risk of VTE between different COCs, provide strong evidence that the risk of VTE is similar to the other COCs studied. Additional evidence from the German case-control and the LASS studies further support these conclusions. All available data on YAZ also align with the finding that DRSP-containing COCs carry a similar risk of VTE compared to other COCs. The studies that have reported an increased risk of VTE for Yasmin compared to LNG-containing COCs have important study design limitations and have failed to appropriately address and control for the known biases that undermine the comparative assessment of the risk of VTE among COCs. The current body of rigorous scientific evidence strongly supports a favorable benefit-risk profile for DRSP-containing COCs when used in accordance to labeling.

2. Introduction

The FDA has convened an Advisory Committee to discuss the risk of VTE associated with the use of DRSP-containing COCs and this briefing document provides background information to better understand the issues surrounding the risk of VTE and its possible association with COC use overall as well as specifically with DRSP. Additionally this document provides details of study results by Bayer and others and their implications in the postmarketing study setting.

There are a number of COCs that contain the estrogen EE and the progestin DRSP ([Table 2-1](#)). Yasmin is approved to prevent pregnancy. YAZ is approved: 1) to prevent pregnancy, 2) to treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception and 3) to “treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control. Safyral and Beyaz incorporate the addition of folate respectively in Yasmin and YAZ, with the additional indication to “raise folate levels in women who choose to use an oral contraceptive for contraception.”

Table 2-1: Components of DRSP-Containing Oral Contraceptives Approved in the US

	DRSP	EE	Hormone Treatment Days	Hormone Free Days	Levomefolate Calcium	Summary of Indication(s)
Yasmin (+generics)	3 mg	0.03 mg	21	7	No	Contraception
Safyral	3 mg	0.03 mg	21	7	0.451 mg	Contraception + Raise folate levels
YAZ (+generics)	3 mg	0.02 mg	24	4	No	1. Contraception 2. (1)+ PMDD 3. (1)+ Acne
Beyaz	3 mg	0.02 mg	24	4	0.451 mg	1. Contraception 2. (1)+ PMDD 3. (1)+ Acne 4. (1) + Raise folate levels

DRSP = drospirenone, EE = ethinyl estradiol, PMDD = premenstrual dysphoric disorder

The following briefing document includes a regulatory history for DRSP-containing OCs ([Section 3](#)), reviews and critiques of the relevant observational studies ([Section 4](#)), review of the mechanism of action ([Section 5](#)), clinical development including efficacy and safety of Yasmin ([Section 6](#)) and YAZ ([Section 7](#)), and overall conclusions ([Section 8](#)).

DRSP-containing COCs are among the most extensively studied COCs both in clinical development and in postmarketing commitment safety studies. The data generated



through Bayer's postmarketing commitment safety studies provide strong evidence that the risk of VTE is similar to the other COCs studied, including LNG-containing COCs. Additionally, it is the sponsor's position that the current body of rigorous scientific evidence strongly supports a favorable benefit-risk profile for DRSP-containing COCs when used in accordance to labeling.

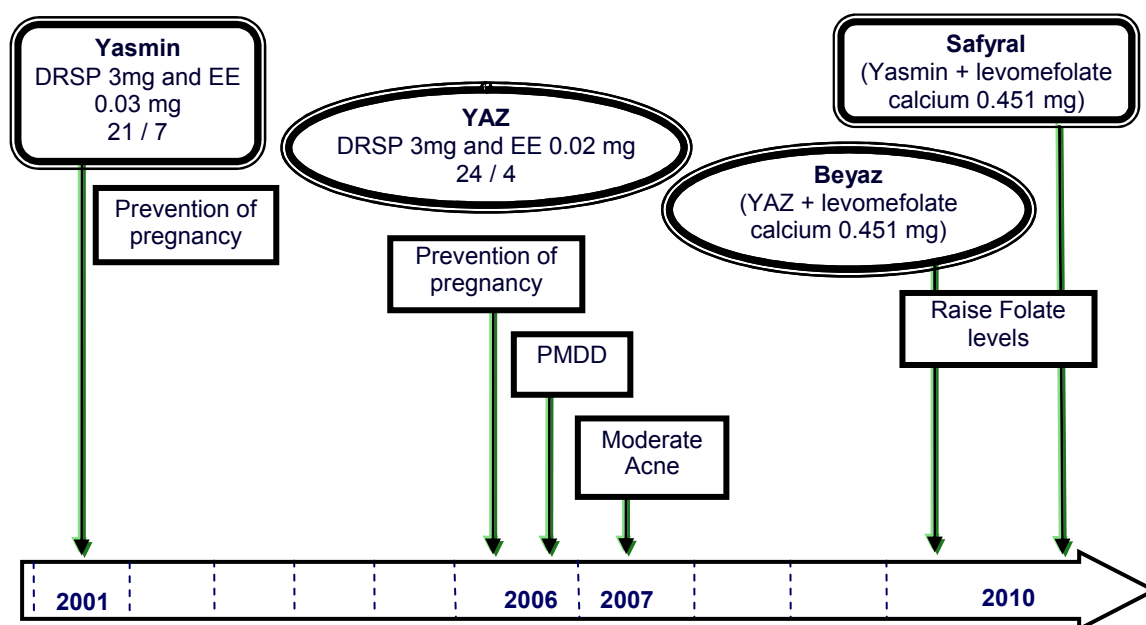
3. Regulatory history

Yasmin was the first DRSP-containing COC approved in the US, and the rest of the world. The US approval was in 2001, for the prevention of pregnancy in women who elect to use an oral contraceptive (Figure 3-1). Yasmin is currently approved in over 130 countries. There is one approved generic of Yasmin in the US, Ocella (TEVA pharmaceuticals) approved in May 2008.

YAZ was approved for the primary indication of contraception in 2006 and the secondary indications of PMDD (2006) and moderate acne (2007) (Figure 3-1). YAZ is currently approved in 107 countries. There is one approved generic of YAZ in the US, Gianvi (TEVA pharmaceuticals) approved in March 2009.

Levomefolate calcium was added to both Yasmin, known as Safyral, and YAZ, known as Beyaz, both with US approvals in 2010, for the secondary indication of raising serum folate levels (Figure 3-1). There are no generic preparations for either Safyral or Beyaz.

Figure 3-1: Drospirenone Containing Oral Contraceptives – US Approvals and Indications



3.1 Yasmin

3.1.1 Postmarketing commitment studies (US and EU)

The original Yasmin label provided guidance for the management of women taking Yasmin, relative to the antimineralocorticoid properties of DRSP. These contraindications, warnings and precautions remain unchanged to this day. The FDA and

the sponsor agreed that it was important to ensure that the recommendations from the label were appropriately integrated into clinical practice and implemented by clinicians. In order to assess the situation, the sponsor agreed to a postmarketing commitment study. This was the subject of the US protocol entitled, “Dispensing Practices, Health Outcomes, and Pregnancy Outcomes in Women Taking Yasmin “ and was submitted in August 2001 after reaching agreement with the US FDA. This prospective, observational study of Yasmin users and matched cohort of other OCs was conducted by a group of independent external investigators (Ingenix), and is referred as the “Ingenix study.” In June 2003, the FDA requested that the sponsor add codes to the Ingenix study to detect thrombotic events, such as PE, stroke, DVT, and retinal vein thrombosis. The investigators, upon request from the sponsor, amended the postmarketing study commitment protocol to comply with the FDA request in February 2004.

In Europe, the regulators were primarily focused on the risk of VTE, against the background of concerns relative to the risk of VTE with any newly introduced COC. Following requests from several Member States during the 2000 approval process of Yasmin in Europe, the sponsor outlined plans for an Active Post Marketing Surveillance Study. This prospective, large-scale cohort study, EURAS, was conducted by independent investigators, and agreed upon with regulatory authorities in Europe.

The interim reports for Ingenix and EURAS were submitted to the US FDA beginning in July 2004 and continued until the submission of the final reports in June 2006.

3.2 YAZ

3.2.1 Postmarketing commitment study (US and EU)

The US approval letter for the prevention of pregnancy NDA confirmed the postmarketing study commitment from the sponsor. This study, intended to be conducted in both the US and Europe, and following the protocol used in the EURAS study, was the INAS study, noted as “INAS-OC.” The same postmarketing commitment was made to the European regulatory agencies, using the same protocol. The objective of this study is to assess the risks of short and long-term use of YAZ (DRSP 3 mg/EE 0.02 mg, 24 day regimen) and of established OCs in a study population that is representative of the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes including: DVT, PE, acute myocardial infarction (AMI), and cerebrovascular accidents. The study is ongoing and interim reports have been submitted to the US FDA beginning in June 2007.

3.2.2 Labeling History Relative to the Risk of VTE with COCs

As noted above, the final study reports for the Ingenix and EURAS-OC studies were submitted to the FDA in 2006 and published in 2007. There was no label change linked to the submission of either study.

In October 2009, the sponsor submitted information to the FDA on the Lidegaard et al. and the Van Hylckama Vlieg A et al. 2009 BMJ publications. These studies evaluated the risk of VTEs associated with the use of Yasmin.

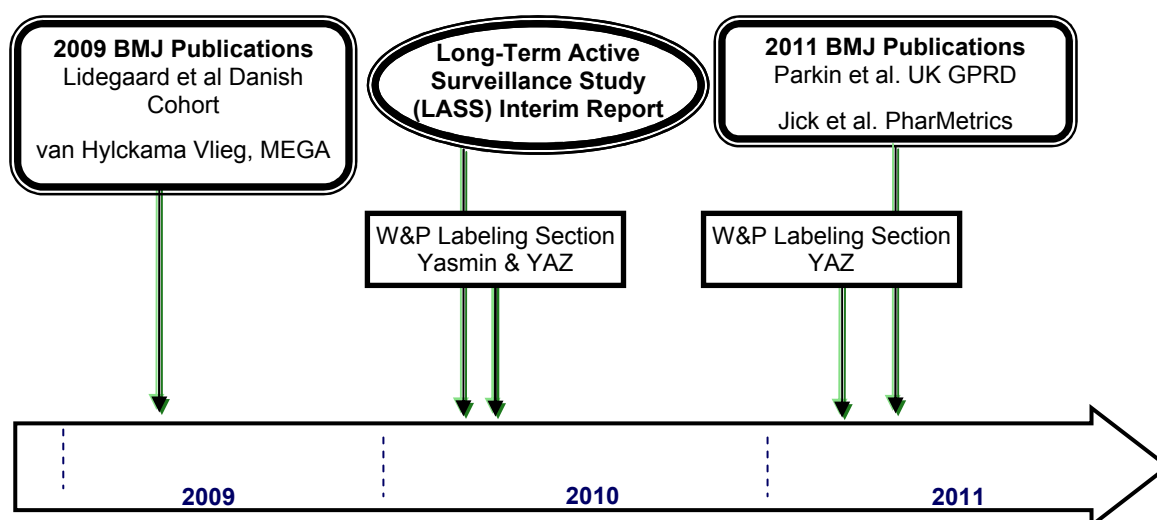
In February 2010 a Prior Approval Supplement was submitted to the YAZ NDA based on the LASS interim results. This supplement was approved in March 2011 and again updated the WARNINGS and PRECAUTIONS section of the US prescribing information. The table below contains the agreed upon wording of this labeling revision.

Prior Approval Supplements, which include results from the interim LASS study, were submitted for the other DRSP-containing OCs (Yasmin, Beyaz, and Safyral). These supplements are currently under review by the US FDA.

In April 2010, the US FDA solicited a label change from the sponsor, which resulted in the WARNINGS and PRECAUTIONS section of US prescribing information being updated for Yasmin and YAZ. [Table 3-1](#) contains the wording agreed upon with the US FDA and approved in April 2010.

[Figure 3-2](#) depicts the submission of sponsor's scientific analysis of the 2009 and the 2011 BMJ publications, LASS, and the 2010 and 2011 labeling approvals.

Figure 3-2: Submission by the Sponsor of the Internal Scientific Analysis of the 2009 and the 2011 BMJ Publications, LASS, and the 2010 and 2011 Labeling Approvals



The WARNINGS and PRECAUTIONS section was updated as described in [Table 3-1](#).

Table 3-1: Updates to the Warnings and Precautions Sections of Prescribing Information

Product	Approval Date	WARNINGS and PRECAUTION Section of Prescribing Information
Yasmin ¹ YAZ Beyaz Safyral	April 2010 April 2010 September 2010 December 2010	<p>“Several studies have investigated the relative risks of thromboembolism in women using Yasmin compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval. The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel. The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COC users, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.</p> <p>Two additional epidemiological studies, one case-control study (van Hylckama Vlieg et al.) and one retrospective cohort study (Lidegaard et al.) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs (so-called second generation COCs) and lower than that for users of desogestrel (DSG)/gestodene-containing COCs (so called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases making the risk estimates unreliable). The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.”</p>

(continued)

¹ See [Section 10.3 \(Appendix 3\)](#) for the approved US labeling for Yasmin, YAZ, Beyaz and Safyral

Table 3-1: Updates to the Warnings and Precautions Sections of Prescribing Information (continued)

Product	Approval Date	WARNINGS and PRECAUTION Section of Prescribing Information
YAZ	March 2011 ²	<p>“The risk of VTE is highest during the first year of use. Interim data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Interim data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.”</p>

Conclusion:

Since 2001, there have been four approvals for DRSP-containing COCs: Yasmin, YAZ, Beyaz, and Safyral. The overall benefit-risk profile of each of these COCs is favorable and aligns with the general class of COCs, including LNG-containing COCs, when used in accordance with the product labeling. The current US labels (see [Section 10.3 \[Appendix 3\]](#)) appropriately convey the overall benefit-risk profile for each of the DRSP-containing COCs currently approved.

² Efficacy supplement based on interim data from LASS

4. Relevant observational studies

4.1 Background information

4.1.1 Venous thromboembolic event

Thromboembolism (TE) is the presence of coagulated blood, a thrombus, in a major blood vessel, either an artery (ATE) or a vein (VTE). DVT refers to a VTE in one of the major deep veins, usually in the leg or arm. Thrombus formation in a major blood vessel of the lung (usually arterial) is referred to as a PE. It is generally acknowledged that DVTs constitute 60-70% of cases of VTE, while PEs account for about 25%, and the remainder of cases involve both DVT and PE.

Classic signs of DVT include pain and limb edema, unilateral or bilateral, but symptoms are highly variable. Even with patients presenting with classic symptoms, nearly half will have a negative diagnostic work-up. Conversely, nearly 50% of patients with image-documented VTE do not complain of symptoms suggestive of a DVT. Therefore, diagnostic tests must be performed whenever the diagnosis of DVT is being considered.

The American Academy of Family Physicians and the American College of Physicians provide 4 recommendations for the workup of patients with suspected VTE ([Qaseem et al., 2007](#)):

1. Validated clinical prediction rules should be used to estimate the pretest probability of VTE and interpret test results.
2. In appropriately selected patients with low pretest probability of DVT or PE, an appropriate next step is to obtain a high-sensitivity D-dimer. A negative result indicates a low likelihood of VTE.
3. In patients with intermediate to high pretest probability of lower-extremity DVT, ultrasonography is recommended.
4. Patients with intermediate or high pretest probability of PE require diagnostic imaging studies in the form of a ventilation-perfusion (V/Q) scan, multidetector helical computed axial tomography (CT) or pulmonary angiography.

In summary, DVT and PE present a serious diagnostic challenge that requires a systematic approach to rule-in or rule-out the diagnosis.

The incidence of VTE increases with age and predominantly affects individuals older than 40 years. Estimates for the rate of VTE among women of reproductive age are quite variable. Dinger et al report an event rate of 4.4 VTE/10,000 WY (95% CI 2.4-7.3), in non-user and non-pregnant women from Germany ([Dinger et al., 2007](#)). A 2007 review of the published literature ([Heinemann and Dinger, 2007](#)) reported rates for non-OC users (and non pregnant women) ranging from 0.3 to 5.3 per 10,000 WY, with one outlier study from 1971 reporting a rate of 16 per 10,000 WY ([Fuertes-de la Haba et al., 1971](#)).

VTE accounts for significant maternal and fetal risks in pregnancy. Pregnancy is generally quoted as being associated with a six fold higher incidence of VTE compared with age-matched nonpregnant women. A study by Heit et al (2005) is often quoted for providing an overall rate of VTE during pregnancy of 20 per 10,000 WY (Heit et al., 2005). The risk of VTE during pregnancy and the postpartum has been assessed in a number of studies and the topic has been systematically reviewed by Jackson et al (Jackson et al., 2011). The authors highlight a nearly universal challenge in the area of studies, whether ascertaining event rates or reporting relative risks:

“Using the baseline incidence rates of venous thromboembolism in nonpregnant, nonpostpartum, reproductive age women reported by Ros et al, Heit et al, Lidegaard et al, and Heinemann and Dinger, we found that incidence rates in women during the first 6 weeks postpartum were 2.5-times to 21.5-times that of nonpregnant, nonpostpartum women, depending on the study. Estimates of baseline incidence rates vary widely (2.4-10/10,000 woman-years), although most were less than five per 10,000 woman-years.”

“However it is important to note that all baseline estimates included in this review are much higher than those assumed by the European drug authorities for nonusers of oral contraceptive pills (0.5-1.0 per 10,000 woman-years), values that have been commonly used to estimate the increased risk of venous thromboembolism posed by use of these pills.”

PE remains a leading cause of maternal mortality (Eldor, 2001; Gherman et al., 1999). In the US, death from PE occurs in 0.2 in 10,000 deliveries and represents 11% of maternal deaths (Andres and Miles, 2001). Postpartum DVT occurs more frequently than antepartum DVT, with reported rates of 0.61 in 1,000 and 0.13 in 1,000 pregnancies respectively (Kierkegaard, 1983).

As highlighted in the FDA drug safety communication (May 31, 2011), “The risk of VTE in users of birth control pills is low, although it is higher than the risk of VTE in women who do not take birth control pills. The risk of VTE in pregnant and postpartum women (about 20 to 30 cases per 10,000 women) is even higher than that in women who take birth control pills” (Heit et al., 2005). The overall benefit-risk of COCs, as a form of effective contraception, is well established and recognized.

4.2 VTE risk factors to be considered in the clinical setting

VTE is a multifactorial condition involving several genetic and/or acquired risk factors. Known risk factors for developing VTE include (Beckman et al., 2010; Geerts et al., 2008):

- Increasing age
- Obesity
- Family or personal history of VTE
- Acquired or inherited thrombophilias (eg, Factor V Leiden, prothrombin G20210A mutation, deficiencies in Protein C, Protein S, or antithrombin)
- Antiphospholipid antibodies

- Chronic disease (eg, cerebrovascular, coronary artery diseases)
- Cancer (active or occult) / cancer therapy (eg, hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)
- Trauma (major trauma or lower-extremity injury)
- Invasive / major surgeries
- Immobilization
- Hospitalization
- Pregnancy / Postpartum period
- Estrogen-containing OCs / Hormone replacement therapy

VTE is a well recognized but rare complication associated with the use of COCs, as a class of drugs. As stated in the most recent labels (PLR format) across current COCs, the expected frequency for VTE is in the range of 3-9/10,000 WY, with the risk being highest during the first year of use.

In addition to a contraindication during pregnancy, the current label for COCs clearly indicate that COCs should not be prescribed to women at a high risk of arterial and venous thrombotic diseases who are known to have the following:

- Smoke, if over age 35
- Have DVT or PE, now or in the past
- Have cerebrovascular disease
- Have coronary artery disease
- Have thrombogenic valvular or thrombogenic rhythm disease of the heart (eg, subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
- Have inherited or acquired hypercoagulopathies
- Have uncontrolled hypertension
- Have diabetes mellitus with vascular disease
- Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35

Across all COC labels, a box warning discusses the relationship between cigarette smoking and serious cardiovascular events. Specifically, the bolded warning points out that the risk of serious cardiovascular events associated with COC use is increased in women who smoke. The risk increases with age, especially in women over 35 years old, and with the number of cigarettes smoked. Therefore COC use is contraindicated in women who smoke and are over age 35.

The Warnings and Precautions section of COC class labeling further elaborates on the risk of thromboembolic disorders and other vascular events. The label clearly states that the use of COCs is associated with increased risk of VTE, as well as ATE, especially in women with other risk factors for these events. For example, women with cardiovascular disease risk factors should use COCs with caution. The risk of cerebrovascular events (thrombotic and hemorrhagic strokes) is increased with COC use, but the risk is greatest in hypertensive women over 35 years of age who also smoke. Additionally, the label provides guidance that women should discontinue COCs at least 4 weeks before and

through 2 weeks after major surgery or other surgeries known to have increased risk of TE, and that COC use should not begin or resume earlier than 4 weeks after delivery (in women not breastfeeding).

While these risk factors are well-recognized and acknowledged, the contribution of each of these risk factors to the increased risk of VTE cannot yet be quantified. It is unclear at this time whether the presence of multiple factors elevates the overall risk of VTE any more than the most serious risk factor present, whether in an additive or synergistic fashion. Accordingly, health care providers must exercise clinical judgment when determining patient eligibility for a COC based upon these contraindications.

Any study into the risk of VTE of COCs must consider these risk factors and control adequately for them.

4.3 Biases to be considered in observational studies comparing the risk of VTE

The first COC approved in the US, in 1960, contained a high dose of estrogen (0.150 mg mestranol, a prodrug of EE), and 9.85 mg norethynodrel, a progestin. Over time, newer preparations were introduced with lower doses of estrogen and progestin. The progressive introduction of lower dose estrogen COCs clinically led to the observation that the risk of VTE was related to the dose of estrogen. Rates of VTE continued to decline with lower doses of EE. Eventually, a marked advantage for COCs with less than 0.05mg of EE was established in terms of the risk of VTE. These so called “low-dose COCs” are now the most widely used form of COCs in the US and around the world. All DRSP-containing COCs are low-dose COCs.

Since the 1980s the focus of research has been to assess the risk of VTE linked to even lower doses of EE within the category of low-dose COCs (eg, 0.03 vs. 0.02 vs. 0.01 mg of EE) and the potential contribution of different progestins to the risk of VTE. While these research efforts are still ongoing, a number of factors have now been identified which must be taken into account in all observational studies comparing the risk of VTE between different COCs.

These biases include:

1. Duration of use/pattern of use
2. Attrition of susceptibles / healthy user effect
3. Prescription bias (channeling)
4. Validity of diagnosis for VTE
5. Referral/diagnostic bias for VTE

4.3.1 Duration of use/Pattern of use

The risk of VTE is highest during the first year of use of COCs (Figure 4-1).

Figure 4-1: Combined Oral Contraceptives: Data from the Transnational Study

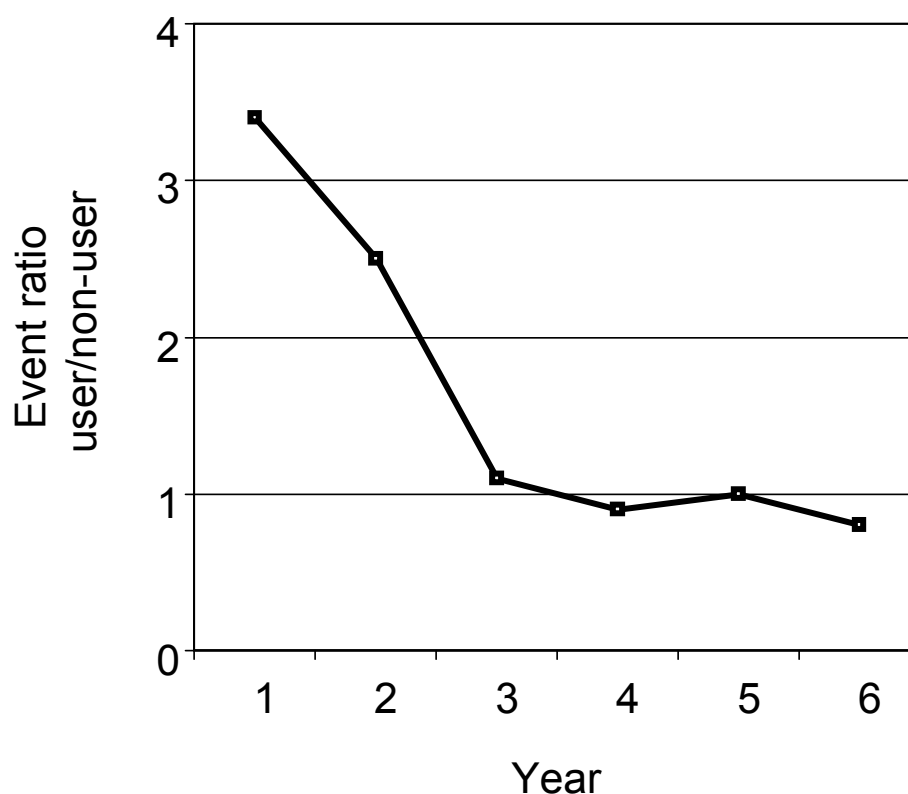


Figure adapted from ZEG (personal communication)

Duration of use is important as a potential source of bias in observational studies attempting to assess the risk of VTE in users of COCs. Lidegaard, Edstrom, and Kreiner (1998) noted that inadequate control for duration of use may lead to an overestimation of the risk of VTE of one COC compared to another (Lidegaard et al., 1998), P.299. In an attempt to control for duration of use, Suissa et al stratified COC use by periods corresponding to <1, 1–2, 2–5 and > 5 years of use (Suissa et al., 1997). Prior to this stratification, a differential risk of VTE was found between different COCs. Following stratification by duration of use with these four strata, the difference was no longer seen, underlining the importance of controlling for this potential bias in observational studies.

With one exception (Poulter N.R, 1995), most studies from the mid 1990s comparing the risk of VTE between different COCs reported a decrease in the odds ratio for VTE in all users of COCs relative to non-users with increasing duration of use. The finding of an increased risk of VTE during the first year of use has been replicated in recent studies (Dinger et al., 2007; van Hylckama Vlieg et al., 2009).

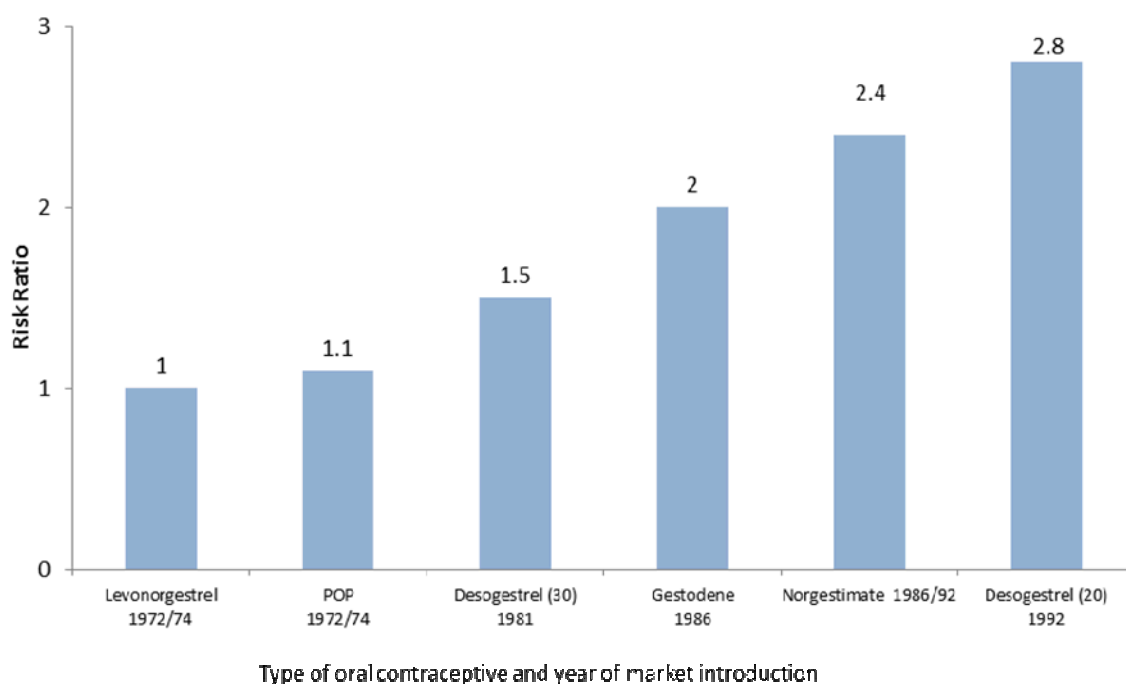
The specific pattern of use, ie, repeat (intermittent) use, switching or first ever use, also influences the risk of VTE, with an increased risk of VTE upon resuming COC use. Failing to account for the pattern of use suggested a different risk of VTE between COCs containing different progestins, while appropriately accounting for pattern of use found similar VTE risks for all the COCs studied. (Lewis et al., 1999; Suissa et al., 1997)

There is, therefore, strong evidence that the risk for VTE is highest during the first year of use. Any study must appropriately control for duration of use. This is critical to ensure that reported higher rates of VTE with a specific COC are not actually due to a higher proportion of new users of that COC in the sample.

4.3.2 Attrition of susceptibles / Healthy user effect

Women who use a COC for the first time ever may have an unrecognized predisposition to VTE at the time, including inherited thrombophilias. Because of this, a population of first-time ever COC user is at a higher risk for VTE overall. Conversely, women who have previously used COCs, and continue to use COCs, represent a lower risk group for VTE, other things being equal. Cross-sectional comparisons of two groups using medications with different market entry points are therefore likely to overestimate the relative risk associated with the most recently introduced medication.

Figure 4-2: Risk Ratios of Combination Oral Contraceptives Containing Specified Progestagens Compared with Levonorgestrel for Women Aged 25-44 Years by Year of Market Introduction



adapted from Lewis et al. (Lewis et al., 1996)

Lewis et al. (Lewis et al., 1999) attempted to avoid the confounding effect of attrition of susceptibles by obtaining data on lifetime COC use for both the cases and the non-cases in their dataset and adjusting for pattern of use. Their analysis showed no evidence for an increased risk of VTE between COCs that had previously been reported to carry a different risk of VTE.

Therefore, any study comparing the risk of VTE for COCs should take into account the lifetime and recent pattern of use, as well as underlying health status of the treatment groups compared.

4.3.3 Prescription bias (Channeling)

Prescription bias occurs when there is selective prescription of drugs depending on the characteristics of the patients. If a drug is perceived as having a better safety profile, doctors may preferentially prescribe it to patients at higher risk, thereby artificially increasing the risk of adverse outcomes associated with that drug.

Newly introduced COCs in the mid 1990s were preferentially prescribed to women at higher risk of VTE, including those with a history of VTE (Heinemann et al., 1996), a family history of VTE (Heinemann et al., 1996; Lidegaard, 1997), obesity (Farmer et al., 1997; Heinemann et al., 1996), chronic inflammatory diseases (Heinemann et al., 1996) and women in older age groups (Farmer et al., 1997; Heinemann et al., 1996; van Lunsen, 1996). In addition, they were preferentially prescribed to first ever users (Heinemann et al., 1996; Jamin and de Mouzon, 1996; Lidegaard, 1997; van Lunsen, 1996).

Two surveys of doctors (UK, Germany), carried out shortly after the 1996 statement from the UK Committee on the Safety of Medicine on the risk of VTE with COCs, showed that doctors reported that they had preferentially prescribed 3rd rather than 2nd generation COCs to women with a family history of VTE (Dunn et al., 1998; Heinemann et al., 1996). Two other studies also found that doctors reported that they would avoid 2nd generation COCs and favor 3rd generation products in women with characteristics thought to be predisposing to VTE (Jamin and de Mouzon, 1996; van Lunsen, 1996). Thus, compelling evidence documents prescription bias.

4.3.4 Validity of diagnosis for VTE

Identifying true cases of VTE in databases, without validation by medical chart review, represents a significant challenge. It is recognized that objective testing for DVT confirms only 20-30% of suspected patients referred for testing (Soehne, 2009). It is therefore important to know the outcome of all referrals and diagnostic tests. This principle was stated clearly as early as 1997, when Jick stated that “Unless one examines clinical records, it is impossible to ascertain whether a case of VTE has been documented by diagnostic tests (ie whether it is in fact a case), nor is it possible to establish with confidence whether it is idiopathic.” (Jick et al., 1997)

Grimes (2011) pointed out the high rate of misclassification that can occur in a database study. In his review of a study of VTE by Lidegaard (Lidegaard et al., 2002), utilizing the

Danish National Patient Registry: of 1660 potential cases, 51 diagnoses were invalid when reviewed by the respective hospital department. Upon questioning the patients, it was discovered that an additional 95 diagnoses were invalid, 80 “cases” were pregnant at the time of the event (despite coding indicating they were not), and 52 had a previous VTE or other thrombotic disease (though these factors were reportedly screened out in the database). (Grimes, 2011).

4.3.5 Referral bias / Diagnostic bias

Women who use COCs that are new to the marketplace, or COCs that become flagged (eg, through news or professional media) as potentially carrying an increased risk of VTE, are more likely to be referred for an evaluation for VTE when expressing clinical complaints compatible with VTE. This is an element difficult to control for outside of a double-blinded randomized clinical trial, but it must still be considered in any open-label observational study comparing the risk of VTE between COCs.

“Referral bias” occurs when patients given the same presentation of history, signs and symptoms, but with different drug exposures have different rates of referral to care. “Diagnostic bias” occurs when, given the same presentation of history, signs and symptoms, a condition is more likely to be diagnosed depending on the exposure history. There is considerable evidence for referral and diagnostic bias for COC users compared with non-users: women with symptoms potentially indicative of VTE who are on COCs are more likely to be referred for further investigations than are women with similar symptoms who are not on COCs (Collet et al., 1994). Barnes et al (1978) found that the rate of confirmed DVT in users of COCs was approximately half that of nonusers, also suggesting many of these women were referred for testing based on the fact they were COC users demonstrating a strong referral (diagnostic suspicion) bias (Barnes et al., 1978).

As Poindexter (Poindexter, 1997) points out, many of the early studies of VTE in COC users assessed cases that came almost exclusively from hospitalized patients with nonfatal VTE. In the 1995 GPRD study, for example, of the 80 cases of hospitalized VTE identified, 42 were DVTs and 38 were PEs (Jick et al., 1995). This proportion of DVT to PE is in contrast to most clinical studies that show that, in the absence of autopsy data, the incidence of clinically diagnosed DVT is approximately twice that of PE (White, 2003). In addition to missing a large number of non-hospitalized VTEs, reliance on hospital only data can potentially introduce a Berkson’s, or admission rate, bias. This can occur if women using a newly introduced COC, given the same presentation of history, signs and symptoms, were more likely to have been hospitalized than women using older preparations. This issue is covered in more detail below. Assessing hospitalized cases alone also ignores the large number of women treated for VTE outside of the hospital.

A survey by Heinemann et al (Heinemann et al., 1996) in Germany suggested that doctors were more likely to refer women with a positive history of VTE or arterial thrombosis who were obese, who had varicose veins or were first time COC users. As already pointed out, these were also the women more likely to be prescribed COCs containing 3rd generation progestins. The group of Heinemann et al. (Heinemann et al., 1996) concluded that referral behavior may act differentially because it is affected *indirectly* by the

different risk profiles of the users of different types of COCs which lead to both channelling to and more ready referral of higher risk women.

4.3.6 Conclusion

No observational study methodology or design achieves perfection. However, the more sources of bias relevant to a specific scientific question that can be accounted for appropriately, the more likely a study is to produce results similar to what would have been obtained in a blinded, randomized trial. The systematic disregard to account for these key sources of bias may yield widely divergent results within the same dataset and consistently erroneous conclusions.

4.4 Specific issues relating to the risk of VTE with DRSP-containing COCs

4.4.1 Mechanism of action – biological plausibility

The risk of VTE that may be attributable to the use of COCs is a class effect related to the estrogen, primarily ethinyl estradiol in current COCs. Furthermore, this relationship has been integrated into clinical practice ascribing a lower risk of VTE for preparations containing less than 0.05 mg of EE (“low dose”) ([Vern L. Katz, 2007](#)). All of the current DRSP-containing COCs are low-dose COCs, with 0.03 mg of EE for Yasmin and Safyral, and 0.02 mg of EE for YAZ and Beyaz.

Progestins are not associated with VTE. No preclinical or in-vitro model supports a differential VTE risk when comparing progestins, either on their own or in combination with an estrogen.

Coagulation or other hemostasis tests are not predictive of the risk of developing VTE with COCs. The mean changes seen in coagulation studies with COCs fall within the range of normal values for healthy reproductive age women. A proposed surrogate endpoint is only helpful in elucidating cause and effect and deemed clinically relevant if validated and proven to have predictive value ([Grimes et al., 2010](#)). This is definitely not the case for the currently available battery of serum coagulation markers. This situation has also been acknowledged by the EMA. The EMA’s revised guideline for the development of steroid contraceptives in July 2005 states that “there are no generally accepted surrogate endpoints for the risk of cancer, cardiovascular events or venous thromboembolism (VTE)” (EMA / CPMP, 2005).

Four studies (three with Yasmin, one with YAZ) evaluated the effects of DRSP COCs on several coagulation tests. One of them, a phase 4 Yasmin study was a cross-over study comparing Yasmin to a LNG-containing COC (Microgynon [0.03 mg EE / 0.150 mg LNG]). The hemostasis measurements in all of these studies included: Factor VIII, fibrinogen, protein C, antithrombin III and activated protein C, and APC resistance. Overall, the changes from baseline were compatible with those seen for COC as a class of drugs. All the changes still were within the normal range of values for reproductive-age women and not clinically meaningful.

Sex hormone-binding globulin (SHBG), a transport protein for sex hormones, has been offered by some investigators as a potential non-hemostatic surrogate marker for the risk of VTE. Some authors have contended that levels of SHBG, the production of which is stimulated by estrogens, and the amount of which can vary depending on the binding affinity of different progestins, may reflect the relative “estrogenicity” of various COCs. This theory holds that the progestin component may result in a decrease in the amount of circulating SHBG that would otherwise have been achieved if the estrogen had been unopposed. Differences in SHBG levels have been demonstrated with use of COCs containing different progestins, with elevations being more pronounced for some (the gonane derivatives norgestimate (NGM), gestodene, and DSG) and antiandrogenic progestins, such as DRSP, relative to those caused by LNG-containing COCs. More recent data generated for COCs containing natural estradiol (E2) instead of EE has shown that although those COCs had a distinctly lower impact on hemostasis variables when compared to a COC containing EE, no difference was found with regard to the SHBG levels. This indicates that SHBG is not linked to the hemostasis system. ([Stanczyk and Grimes, 2008](#); [van Vliet HA, 2009](#)). A relationship between changes in hemostatic markers or in SHBG levels and the clinical endpoint of VTE has not been established.

4.5 Information from clinical trials in the development program

A total of 16 clinical studies provided tolerability and safety data on Yasmin and Safyral prior to approval. Based on the analysis of the clinical studies to investigate the tolerability and safety of Yasmin as a COC and the premenstrual syndrome (PMS)/PMDD and folate studies, a total of 4,421 women were included in the overall safety assessment, among them 3,028 women treated with Yasmin, Yasmin + folic acid, or Safyral. In accordance with the CPMP Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Diseases (CPMP/EWP/563/98), DVT and PE were considered to be cases of VTEs, but cases of superficial thrombophlebitis were not included.

VTEs were recorded for 1 of 2,699 women treated with Yasmin in the OC studies.

Based on the 14 clinical studies to investigate the tolerability and safety of YAZ, Yasminelle (3 mg DRSP/0.02 mg EE, 21/7; not marketed in the US), or Beyaz in the OC, PMDD, acne, and folate studies, a total of 5754 women were included in the overall safety assessment, among them 4,480 women treated with YAZ, Yasminelle, or Beyaz. Two women in the OC studies treated with Yasminelle had confirmed PE, and another woman on Yasminelle had a suspected thrombosis of the leg.

In summary, the exposure of women treated with Yasmin, Safyral, YAZ, or Beyaz in clinical studies is too limited to adequately quantify the risk of rare events such as VTE. It should be noted that clinical studies for marketing application are not a useful source for evaluating incidence rates of such rare events as they generally include too few women (CHMP ‘Guideline on Clinical Investigation of Steroid Contraceptives in Women’, EMEA/CPMP/EWP/519/98 Rev). Nevertheless, the findings observed for Yasmin and YAZ were in line with the safety profile of other COCs.

4.6 Information obtained through the global pharmacovigilance program

Adverse event data from spontaneous sources have well-known limitations. In their 2005 Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, the FDA remarked “[V]oluntary adverse event reporting ... [is] subject to a variety of reporting biases (eg, some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other comorbidities or unrecorded confounders, may cause the events to be reported). In addition ... data may be affected by the submission of incomplete or duplicate reports, underreporting, or reporting stimulated by publicity or litigation.”

Based on global sales and marketing data (as of 31 August 2011), it is estimated that the total worldwide global exposure to the sponsor’s DRSP-containing COCs covers 62.3 million WY of exposure, with 13.5 million WY of exposure occurring in the US, which includes exposure from two authorized generic products marketed in the US. Postmarketing safety data with Yasmin and YAZ are consistent with the known safety profile of COC products as a class. Based on the available data, no safety signal has been identified and the sponsor’s assessment of the benefit-risk balance is favorable.

Postmarketing safety data with Yasmin and YAZ are consistent with the known safety profile of the products obtained during clinical trials and the postmarketing safety studies. Since 2009 an increasing reporting rate for AEs, in particular VTEs, has been seen, which is primarily related to a large number of served product liability lawsuits. The characteristics of reported AE cases are, however, in line with the safety experience gained from use of COCs, including those containing DRSP. Currently, increased reporting rates reflect both altered reporting behavior and limitations in the quality of received AE reports. It does not provide any evidence for new safety findings related to Yasmin or YAZ.

Based on the available data, no new and/or unexpected safety signal has been identified. The data are consistent with the cumulative experience to date and the reference safety information of the products. The sponsor’s assessment of the benefit-risk balance remains favorable.

4.7 Observational studies on the risk of VTE with Yasmin

Yasmin was approved in Europe in November 2000, followed by a US approval in May 2001. Subsequently, two prospective postmarketing studies were undertaken. The European Active Surveillance (EURAS) study focused mainly on the risk of cardiovascular events including VTE and ATE for Yasmin compared to other OCs in clinical use. The Ingenix study initially assessed compliance with the label in clinical practice and monitored the AE profile relative to the antimineralocorticoid properties of Yasmin. Within two years of its initiation, the study protocol for the on-going Ingenix study was expanded, in consultation with the FDA, to include as a primary endpoint the assessment of the risk of VTE comparing Yasmin to other low-dose COCs, including LNG-containing COCs.

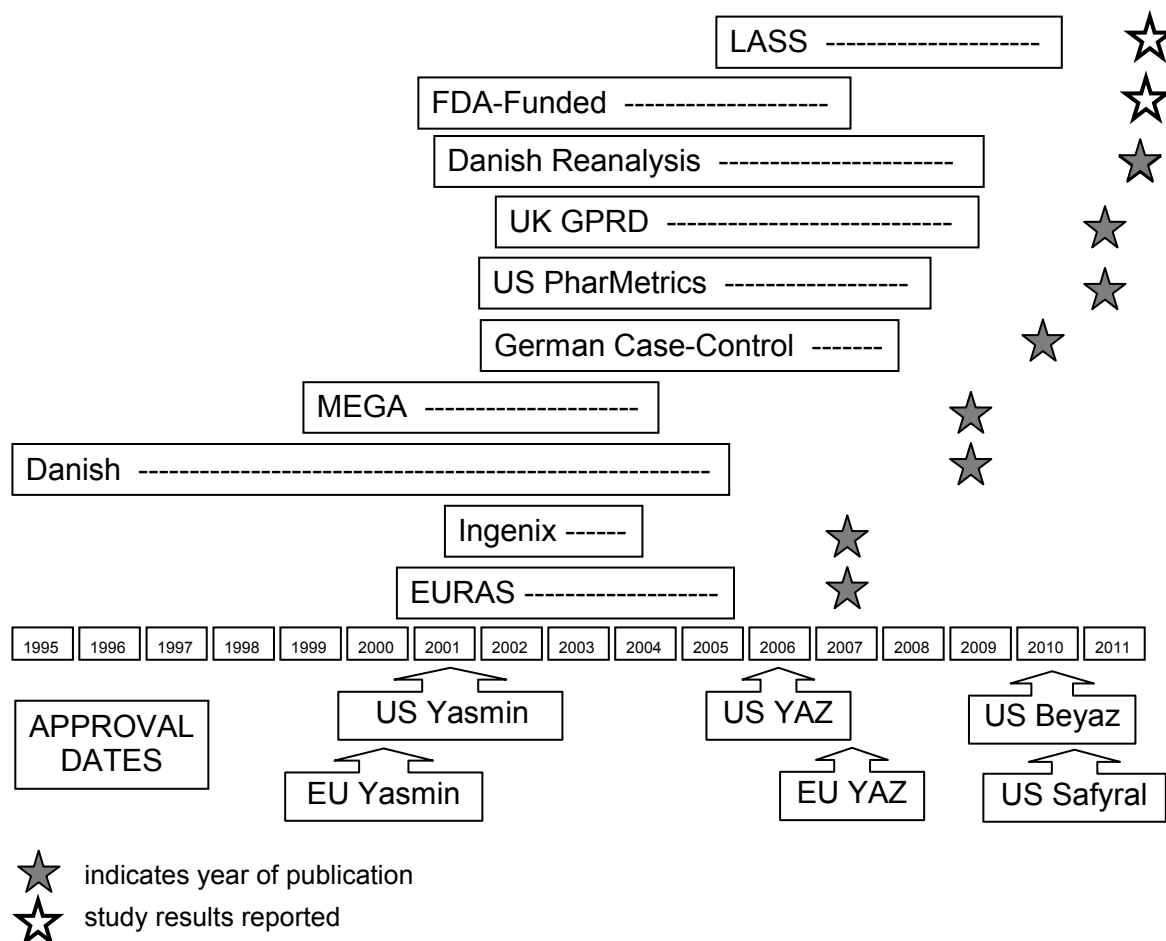
For both of these postmarketing study commitments, the study protocol, amendments, and statistical analysis plans were discussed with and reviewed by the respective regulatory agencies (FDA for Ingenix, EMA for EURAS) and all of these elements were available to the regulatory agencies. Regular interim reports, as well as the full final study reports for Ingenix and EURAS were submitted to the FDA, EMA, and other regulatory agencies around the world. The primary reports on the risk of VTE for both studies were published in peer-reviewed journals, both in 2007 ([Dinger et al., 2007](#); [Seeger et al., 2007](#)). Both studies concluded that the risk of VTE is similar between Yasmin and the other COCs studied, including LNG-containing COCs.

Since 2009 (and as of the time of completion of this Briefing Document), six publications, in peer-reviewed journals, have compared the risk of VTE for Yasmin users to users of other COCs. Two publications appeared in August 2009: the Dutch MEGA study ([van Hylckama Vlieg, Helmerhorst et al. 2009](#)) and the Danish Registries Study ([Lidegaard, Lokkegaard et al. 2009](#)). In both studies, the authors concluded that the risk of VTE with Yasmin was elevated compared to LNG-containing COCs, but less elevated than COCs containing other types of progestins (the so-called 3rd generation progestins such as DSG and gestodene). A third publication, the German Case-Control study, commissioned by the sponsor, appeared in July 2010, with the authors reporting a similar risk of VTE for users of Yasmin compared to other COCs. ([Dinger, Assmann et al. 2010](#)) The fourth and fifth publications are from April 2011: the US PharMetrics study and the UK GPRD study ([Jick and Hernandez, 2011](#); [Parkin et al., 2011](#)). The authors reported on the risk of so-called “non-fatal idiopathic VTE” only and concluded that there was an increased risk of VTE in Yasmin users compared to users of LNG-containing COCs. The sixth publication, from October 2011, consists of a reanalysis of the Danish Registries Study ([Lidegaard et al., 2011b](#)); the authors conclude that this study validates their findings from the 2009 publication. In addition, on 27 October 2011, the FDA posted on its website the report from the study it had commissioned. The authors concluded that the risk of VTE with Yasmin was elevated compared to comparator COCs, as well as LNG-containing COCs ([Ouellet-Hellstrom et al., 2011](#)).

In addition to these peer-reviewed publications and the FDA-funded study report, one additional study has been completed and the results presented here. This study is a follow-up to the EURAS study, LASS, which provides an additional five years of observation on subjects enrolled in the EURAS study. The study was completed in mid-2011 and the final study report was submitted to the FDA in September 2011 ([Dinger, 2011](#)). The results from the LASS study confirm the prior findings from the EURAS study, that the risk of VTE is similar between Yasmin and the other OCs studied, including LNG-containing COCs.

[Figure 4-3](#) presents a timeline of the studies, relative to their publication date, and the time interval they encompass. Provided below are tabular summaries for each study and the sponsor’s assessment of the strengths and limitations of each study. Specifically, the sponsor presents its analysis around how well each study addressed potential biases that must be considered in comparing the risk of VTE between COCs.

Figure 4-3: Timeline of Studies Relative to Their Publication Date and the Time Interval They Encompass



4.7.1 Observational studies

NOTE: Please note that the US package insert reports event rates for VTE using per 10,000 WY as the denominator. Individual studies and reviews vary in how they report this rate, with denominators ranging from per 1,000 WY to per 100,000 WY. For clarity, for each study, we have included a conversion to per 10,000 (or 10^4) WY.

4.7.1.1 Ingenix Yasmin study (Seeger et al., 2007)

The Ingenix study was designed to fulfill a postmarketing commitment to the FDA. This study was commissioned by the sponsor and included Drs. Walker, Seeger and Loughlin as investigators, all with Ingenix. The study protocol was discussed with the FDA. The original protocol, known as the US Ingenix study (“Dispensing Practices, Health Outcomes, and Pregnancy Outcomes in Women Taking Yasmin”) was conducted to assess if the unique antimineralocorticoid properties of Yasmin were related to an increase in

hyperkalemia or related outcomes in the Ingenix database, using a cohort design. In addition, the study evaluated the use of Yasmin among women with contraindications or warnings related to its use to assess compliance of health care providers with the recommendation to measure serum potassium in the first Yasmin cycle among women receiving long-term therapy with drugs that predispose to increased serum potassium. In light of the ongoing EURAS study in Europe, and emerging case reports around the risk of VTE with Yasmin, the FDA requested and the sponsor agreed to amend the Ingenix study protocol to include, as a primary outcome, an assessment of the risk of venous and arterial thromboembolic events compared to the other COCs in the study, including LNG-containing COCs. Interim reports and a full study report (in 2006) were submitted to the FDA and the VTE results were published in the peer-reviewed literature in 2007, as indicated in the table below.

Note: The FDA has requested that the sponsor requests from the research group (now Innovus) a subanalysis from the Ingenix study which has not been provided to date by Innovus. This subanalysis will be submitted to the FDA when available. This subanalysis will provide a breakdown on the basis of the different progestins contained in the other COCs studied in Ingenix, with exposure data by WY for each progestin, and the number of VTE events for each progestin. Note that these data will be crude data as there will be no propensity score matching between treatment groups compared. Thus it will not be possible to draw any valid conclusions of relative risk among the treatment groups.

Table 4-1: Structured Summary of Study Design as Reported by the Authors - Ingenix

INGENIX, Seeger et al. 2007	
METHOD	
Objective	To estimate the association between Yasmin and the risk of VTE relative to the association among other oral COCs.
Study Design	Observational/cohort study
Geography	USA
Time Period	June 2001 – June 2004
Population / Source of Data	Proprietary Research Database (Ingenix) built from electronically captured provider facility and pharmacy claims at United Healthcare affiliated health plans and large employer groups; follow-up in the written medical records Cohorts: women aged 10-59 who received a dispensing of Yasmin after at least 6 months in the health plan without having had a previous dispensing of Yasmin ('Yasmin initiators'), along with women who by the same criteria initiated another OC in the same quarter;
Sample size	Yasmin: 22,429 (14,081 WY) Other COCs: 44,858 (27,575 WY) Average follow-up 7.6 months / Overall 41,656 WY

ASSIGNMENT	
Baseline exclusion criteria	None
Assessment of COC use	All subjects considered new onset users on the basis of no prior COC use in the previous six months. Duration of use ascertained through evidence of prescriptions in database. COC use ascertained via prescription record in database.
Comparator	All other COCs
Method to address confounding	Propensity score matching, conducted separately within each calendar quarter of initiation, creating a close balance between groups with respect to calendar time, medical history, treatment and personal characteristics (>100 characteristics); 2-to-1 matching of other OCs vs. Yasmin. (Publication includes tables which demonstrated that key covariates included in the propensity score were balanced between the matched treatment groups, indicating that the propensity score matching methodology was successful.) A separate validation study undertaken to assess BMI and smoking, which were not included in the database (or the propensity score), suggested that these covariates were balanced between the matched cohorts.

ASSESSMENT	
VTE Definition	Insurance claim data, possibly consistent with the occurrence of TE Process includes fatal cases.
VTE Validation Process	Medical record extraction for all patients whose insurance claims sequence was possibly consistent with the occurrence of TE. Medical records were available for 93% of Yasmin initiators and 85% of other COC initiators. Adjudication by clinician blinded to COC use status. Only validated cases were included.

RESULTS
VTE Event Rates (n): Yasmin 13/10,000 WY (18) / Other COCs: 14/10,000WY (39)
Relative Risk Yasmin versus other COCs: 0.9 (95%CI 0.5-1.6)
INTERPRETATION / Authors' Overall Conclusion
Yasmin initiators and initiators of other COCs are similarly likely to experience TE.

KEY FACTOR	APPROACH
Duration of use/ Pattern of use	6+ months of no prior COC use / Tracked consecutive vs. interrupted use
Attrition of susceptibles/ Healthy user effect	1 st time and recurrent users grouped together / Cohorts balanced for underlying health status through propensity score matching, mitigating the potential 'healthy user effect'
Prescription bias	Balanced for underlying health and risk factors through propensity score matching
Validity of diagnosis For VTE	Clinical chart review / Treatment-blinded adjudicator

Strengths:

- VTE confirmation based on clinical chart review, with treatment-assignment blinded adjudicator, includes fatal cases
- Exposed subjects identified without prior knowledge of outcome (VTE) (prospectively assembled cohort)
- Matched based on exposure (Only new users after at least 6 month off COC).
- Cohort balance achieved in terms of baseline risk through propensity score matching. Propensity scores took into account such factors as age, date of entry into the database, type of reimbursement plan, history of COC use, use of health services, acute and chronic medical conditions, laboratory values and medication usage; an internal validation study revealed no systematic differences in characteristics between cohorts
- US population, observational database study design

Limitations:

- Clinical practice may have given rise to referral and diagnostic bias, which was not accounted for in the study design (bias against Yasmin)
- No direct comparison to LNG-COCs
- No direct adjustment for BMI or smoking
- Unable to distinguish first-ever start from new start or restart
- Only 6 months of prior COC usage data available prior to inclusion in cohort
- Failure to retrieve medical charts (Yasmin 8%, other COCs 15%) potentially led to omission of cases, which would have increased the apparent risk of VTE to the detriment of Yasmin.

The Ingenix study protocol integrated sound principles of study design and the opportunity to appropriately account for most of the potential biases of relevance to comparing the risk of VTE between COCs. Any observational study based on an administrative database is confronted with the limitations of its data source. For example, the restricted time frame in Ingenix does not allow for distinction between first time ever users and restarters in the 'new use analysis'. The Ingenix study sought to achieve balance between the cohorts through the procedure of propensity score matching, using over 100 covariates available in this database. This approach created a close balance between groups with respect to calendar time, medical history, treatment and personal characteristics. The event rates reported in the Ingenix study, slightly higher than

generally reported, are compatible with the early user effect, given the average follow-up of 7.6 months. The risk of underascertainment of VTE cases within the Ingenix study is very low.

Overall, the sponsor views the Ingenix study as providing solid evidence that the risk of VTE with Yasmin is similar to the COCs studied.

4.7.1.2 European Active Surveillance (EURAS) OC Study (Dinger et al., 2007)

As outlined above, upon the approval of Yasmin in Europe, the sponsor agreed with the EMA to conduct a postmarketing commitment study focusing mainly on the risk of cardiovascular events including VTE and ATE for Yasmin compared to other OCs in clinical use. The EURAS study was funded by the sponsor and conducted by the Center for Epidemiology and Health Research, Berlin, Germany (ZEG). Interim reports and a full study report (in 2006) were submitted to the FDA and the VTE results were published in the peer-reviewed literature in 2007, as indicated in the table below.

4.7.1.2.1 Data on VTE

Table 4-2: Structured Summary of Study Design as Reported by the Authors for VTE - EURAS

EURAS, Dinger et al. 2007	
METHOD	
Objectives	To compare risks of adverse cardiovascular and other events associated with the use of Yasmin and other OCs.
Study Design	Observational cohort study – prospective
Geography	7 EU countries (Austria, Belgium, Denmark, France, Germany, Netherlands, and UK)
Time Period	November 2000 to December 2005
Population / Source of Data	Network of physicians who prescribe OCs at 1113 participating centers. All women who received a prescription for a new OC were asked by their physician if they were willing to participate. All women who consented and were either starters (first-ever users) or switchers were enrolled.
Sample size	Overall: 58,674 women (142,475 WY) Yasmin: 16,534 (28,621 WY) LNG COCs: 15,428 (31,415 WY) Other OCs: 26,341 (52,623 WY) Follow-up 1.5-5 years

ASSIGNMENT	
Baseline exclusion criteria	Clinicians chose COC use based on their clinical judgment. No other specific inclusion or exclusion criteria were applied.
Assessment of COC use	Patient self-administered questionnaire at baseline (completed at study site) and every 6 months thereafter. User groups divided according to: First ever users, first use of a new preparation, re-starting a previously used preparation and switching directly from one preparation to another
Comparator	1. LNG COCs 2. All other OCs (including LNG COCs)
Method to address confounding	Risk factors ascertained via patient questionnaire. Stratified analyses based on duration and pattern of use. Adjustment in a regression model for predefined confounding variables age, BMI, duration and pattern of use, and personal and family history of VTE

ASSESSMENT	
VTE Definition	Initial detection based on twice yearly, patient completed questionnaire; Events confirmed by diagnostic measures with high specificity (eg, venogram for DVT) or clinical diagnosis supported by diagnostic test with low specificity (eg, D-dimer). Diagnosis excluded if diagnostic measures excluded the diagnosis, different medical condition diagnosed by a physician, or if no medical attention sought by subject.
VTE Validation Process	All suspected VTE were assessed through the validation process After patient-physician interviews, clinical chart review by 3 treatment-blinded adjudicators. VTE was deemed confirmed if at least 1 adjudicator considered the event as confirmed.

RESULTS
<p>VTE Event Rates (n): Yasmin : 9.1/10,000 WY (26) / LNG-COCs: 8.0/10,000 WY (25) / Other OCs: 9.9/10,000 WY (52)</p> <p>Hazard Ratios (Crude) Yasmin vs. LNG: 1.1 (95% CI 0.7-2.0) Yasmin vs. LNG + Other COCs: 1.0 (95% 0.6-1.6)</p> <p>Hazard Ratios (Adjusted) (for age, BMI, duration of use, VTE history) Yasmin vs. LNG: 1.0 (95% CI 0.6-1.8) Yasmin vs. LNG + Other COCs: 0.9 (95% CI 0.6-1.4)</p>

INTERPRETATION / Authors' Overall Conclusion	
Risk of VTE in Yasmin users is similar to those associated with the use of other OCs.	
KEY FACTOR	APPROACH
Duration of use/ Pattern of use	Groups stratified based specifically on lifetime history of use, duration of use and pattern of use
Attrition of susceptibles/ Healthy user effect	Analysis by groups based on self-reported history of prior use, including first-time ever use cohort
Prescription bias	Key risk factors ascertained by self-reported questionnaire at baseline and updated every 6 months / Analyses adjusted for risk factors
Validity of diagnosis For VTE	Medical records review / Adjudication by 3 exposure-blinded experts

Strengths:

- Community-based observational study
- Ascertainment of events through a self-reported questionnaire administered every six months, documenting exposure and AEs
- Adjusted for predefined confounding factors: age, BMI, history (personal and family) of VTE
- Separate and pre-planned subanalyses based on duration and pattern of use, including first-time ever use; the time-dependent decline of the VTE incidence was similar for all OCs.
- VTE cases confirmed through clinical records review, and adjudication was done by 3 exposure-blinded experts, with high level of agreement (99.4 %) (*info not presented in publication*)
- Loss to follow-up was minimal (less than 3%), with only minor differences between the cohorts (2.4, 2.7 and 2.2 % for DRSP, LNG- and other OC cohorts), indicating that bias due to loss-to-follow-up can be largely excluded.
- Search of governmental records for deaths to ensure all events were captured. (Multi-step algorithm for patient follow-up)

Limitations:

- VTEs and exposures were self-reported by the study subjects and may be influenced by memory.
- The active surveillance process with prompted recall around events compatible with VTE may have driven an increased awareness of symptoms and signs of VTE and reporting. Media attention about the potential increased risk of VTE with Yasmin may have led to a referral/diagnostic bias, which would have increased the apparent risk of VTE to the detriment of Yasmin. The proportion of confirmed diagnosis for VTE was lower among women using Yasmin compared to other COCs (18.2% for Yasmin users, 25.8% for LNG-COC users, and 25.0% for other COC users), supporting this potential bias. (From final study report).
- Diagnosis of VTE was based on local clinical standards, without a pre-specified diagnostic algorithm. Some diagnostic methods for VTE (eg, D-dimer) are known to

have suboptimal specificity (ie, other events besides VTE can elevate D-dimer). This may have introduced a non-differential classification bias (validation of diagnosis) that may have reduced the likelihood of finding a difference between the groups observed.

- Inclusion in study required patient consent

4.7.1.2.2 Data on ATE

Table 4-3: Structured Summary of Study Design as Reported by the Authors for ATE - EURAS

EURAS, Dinger et al. 2007 / ATE DATA	
METHOD – As Described in VTE section above	
ASSIGNMENT	
Baseline exclusion criteria	Clinicians chose COC use based on their clinical judgment. No other specific inclusion or exclusion criteria were applied.
Assessment of COC use	As described in VTE section above
Comparator	As described in VTE section above
Method to address confounding	Risk factors ascertained via patient questionnaire. Adjustment in a regression model for predefined confounding variables: age, BMI, smoking and hypertension for ATE

ASSESSMENT	
ATE Definition	AMI, cerebrovascular accident (CVA), transient ischemic attack (TIA), and other organs and peripheral arteries
ATE Validation Process	<p>Validation as for all serious adverse events (SAEs) in study:</p> <p>Definite Event – to be confirmed by diagnostic measures with high specificity:</p> <p>AMI: typical change of cardiac enzymes with high specificity (creatinine kinase MB fraction [CK-MB], cardiac troponin, glycogen phosphorylase isoenzyme BB) typical electrocardiogram [ECG] changes (eg, ST segment elevation), coronary angiography</p> <p>Stroke: typical clinical signs persisting for days, confirming by imaging with high specificity (eg, CT, magnetic resonance imaging [MRI], cerebral angiography, positron-emission tomography [PET])</p> <p>TIA: typical clinical signs (followed by resolution within 24 hours) and imaging with high specificity and sensitivity (eg, MRI) does not indicate tissue necrosis</p> <p>Other organs and peripheral arteries (eg, kidney, gut, adrenals, femoral artery): confirmed by imaging with high specificity (eg, arteriography, CT, MRI)</p> <p>Probable Event: Absence of confirmation by a diagnostic measure with high specificity, but other evidence pointing in the direction and clinical diagnosis is confirmed by attending physician:</p> <p>AMI: typical clinical symptoms, change of cardiac enzymes with low specificity (eg, creatine kinase [CK], aspartate transaminase [AST], lactic dehydrogenase [LDH]) or indirect ECG signs (eg, ST- segment depression in case of posterior myocardial infarction [MI]), and clinical diagnosis confirmed by attending physician</p> <p>Stroke: clinical signs persisting for days, confirmatory imaging not done or inconclusive, but clinical diagnosis confirmed by attending physician</p> <p>TIA: typical clinical signs followed by resolution within 24 hours, but no imaging with high specificity but clinical diagnosis confirmed by attending physician</p> <p>Other organs and peripheral arteries (eg, kidney, gut, adrenals, femoral artery): confirmatory imaging not done but clinical diagnosis confirmed by attending physician</p> <p>Event not confirmed: Diagnosis reported by the patient was excluded by diagnostic procedures or a different medical condition was diagnosed by a physician, woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis.</p>

Results:

In total, 25 ATEs (mainly stroke and MI) were observed in the study:

Yasmin cohort: 2 events (0.7 events/10⁴ WY; 95% CI: 0.1 – 2.5)

LNG cohort: 9 events (2.9 events/10⁴ WY; 95% CI: 1.3 – 5.4)

Other OCs cohort: 9 events (1.7 events/10⁴ WY; 95% CI: 0.8 – 3.2)

Table 4-4 Adjusted hazard ratios (HR) and confidence limits for ATE and All TE (EURAS study)

	Yasmin versus					
	LNG-containing OCs		Other OCs		LNG & Other OCs	
	HR	95% CI	HR	95% CI	HR	95% CI
ATE	0.3	0.1 – 1.2	0.3	0.1 – 1.5	0.3	0.1 – 1.3
TE ^a	0.9	0.5 – 1.4	0.7	0.4 – 1.1	0.8	0.5 – 1.2

^a all thromboembolic events (VTE and ATE combined)

Numbers are from the Dinger 2007 publication.

The adjustment shown in [Table 4-4](#) is based on Cox regression analysis, using the pre-defined confounder variables for ATE: age, BMI, smoking and hypertension.

Interpretation / Authors' Overall Conclusion:

Overall, all VTE (discussed in prior section), ATE, and TE hazard ratios (adjusted and crude) that compared the Yasmin cohort with other OC cohorts are close to or lower than unity and do not suggest a higher risk for Yasmin users. The narrow confidence intervals suggest that the risk for the 3 cohorts is similar.

Strengths: (retained items from prior sections pertaining to VTE are italicized)

- *Community-based observational study*
- *Ascertainment of events through a self-reported questionnaire administered every six months, documenting exposure and AEs*
- Adjusted for predefined confounding factors: age, BMI, smoking and hypertension
- ATE cases confirmed through clinical records review
- *Loss to follow-up was minimal (less than 3%), with only minor differences between the cohorts (2.4, 2.7 and 2.2 % for DRSP, LNG- and other OC cohorts), indicating that bias due to loss-to-follow-up can be largely excluded.*
- *Search of governmental records for deaths to ensure all events were captured. (Multi-step algorithm for patient follow-up)*

Limitations: (retained items from prior sections pertaining to VTE are italicized)

- *ATEs and exposures were self-reported by the study subjects and may be influenced by memory.*
- *The active surveillance process with prompted recall around events compatible with ATE may have driven an increased awareness of symptoms and signs of ATE and reporting.*
- *Diagnosis of ATE was based on local clinical standards, without a pre-specified diagnostic algorithm. This may have introduced a non-differential classification bias (validation of diagnosis) that may have reduced the likelihood of finding a difference between the groups observed.*
- *Inclusion in study required patient consent*

Few recent studies have focused on the risk of ATE with COCs. Just as it was the case for VTE, the EURAS study is to be among the most rigorous and robust studies ever conducted on the risk of ATEs associated with COCs. The EURAS study provides reassuring evidence that the risk of ATE with Yasmin is similar to the COCs studied, including LNG-containing COCs. The observed trend toward a lower ATE event rate with Yasmin was one of the reasons that prompted the sponsor to prolong the observation period of subjects enrolled in the EURAS study for an additional five years, which became the LASS study.

4.7.1.2.3 Overall conclusions on EURAS

The EURAS study is a large (112,659 WY of exposure in the Yasmin, LNG, and Other OCs cohorts) and well conducted (eg, the very low drop-out rate, 100% validation of outcomes of interest, and blinded adjudication of the final results by study-independent medical experts) study that provides robust results on the occurrence of rare SAEs like VTE and ATE during typical OC use in European women of childbearing age. In particular, the study design and methodology are well suited to deliver precise results on the rates for overall AEs and SAEs, organ-system specific SAEs, overall mortality, outcome-specific mortality and other outcomes.

The sponsor considers the EURAS study to be among the most rigorous and robust studies ever conducted on the VTE risk associated with COCs. The EURAS study is contributing to the science of COCs beyond its primary objectives. For instance, EURAS has confirmed the increased risk of VTE during the first year of use of COCs, but it has further defined that this risk is further concentrated during the first few months of use.

The EURAS study provides compelling evidence that the risk of VTE, and likely ATE, with Yasmin is similar to the COCs studied, including LNG-containing COCs.

4.7.1.3 Long-term Active Surveillance Study (LASS) (Dinger et al., unpublished)

No public dissemination of these data has occurred as of the submission of this Briefing Document.

LASS is a follow up extension of the EURAS study. The LASS study completed in mid-2011 and the final study report of the LASS study was submitted to the FDA in September 2011. Because it is an extension of the EURAS study, it is discussed here.

At the time of submission of this briefing document, the results of LASS have not been published in the peer reviewed literature.

4.7.1.3.1 Data on VTE

Table 4-5: Structured Summary of Study Design as Reported by the Investigators for VTE - LASS

LASS, Dinger et al., unpublished	
METHOD	
Objectives	To compare risks of adverse cardiovascular and other events associated with the use of Yasmin and other OCs; extension of the EURAS study
Study Design	Observational cohort study – prospective
Geography	7 EU countries (Austria, Belgium, Denmark, France, Germany, Netherlands, and UK)
Time Period	November 2000 to December 2005 (EURAS), follow-up for 5 additional years to December 2010 (total of up to 10 years, LASS)
Population / Source of Data	Network of physicians who prescribe OCs at 1113 participating centers. All women who received a prescription for a new OC were asked by their physician if they were willing to participate. All women who consented and were either starters (first-ever users) or switchers were enrolled.
Sample size	58,674 women entered the EURAS study, of which 47,799 entered LASS in Dec 2005; Combined EURAS/LASS database: Exposure: 318,784 WY of observation 216,038 WY of OC exposure Yasmin: 16,534 (52,278 WY) LNG COCs: 15,428 (57,539 WY) Other OCs: 26,341 (106,221 WY) Follow-up 1.5 up to 10 years

ASSIGNMENT	
Baseline exclusion criteria	According to individual clinician judgment for COC use. No other specific inclusion or exclusion criteria were applied.
Assessment of COC use	Self-reported Patient questionnaire. User groups divided according to: First ever users, first use of a new preparation, re-starting a previously used preparation and switching directly from one preparation to another
Comparator	3. LNG COCs 4. All other OCs (including LNG COCs)
Method to address confounding	Risk factors ascertained via self-reported patient questionnaire. Adjustment for predefined confounding variables age, BMI, duration and pattern of use, and personal and family VTE history

ASSESSMENT	
VTE Definition	Initial detection based on twice yearly, patient completed self-reported questionnaire; After first 5 years of study, yearly questionnaires were collected. Events confirmed by diagnostic measures with high specificity (eg, venogram for DVT) or clinical diagnosis supported by diagnostic test with low specificity (eg, D-dimer). Diagnosis excluded if diagnostic measures excluded the diagnosis, different medical condition diagnosed by a physician, or if no medical attention sought by subject. Process includes fatal cases.
VTE Validation Process	After patient-physician interviews, clinical chart review by 3 treatment-blinded adjudicators. VTE was deemed confirmed if at least 1 adjudicator considered the event as confirmed.

RESULTS
<p>VTE Event Rates (n): Yasmin : 10.7/10,000 WY (56) / LNG-COCs: 9.2/10,000 WY (53) / Other OCs: 13.6/10,000 WY (144)</p> <p>Hazard Ratios (Crude) Yasmin vs. LNG: 1.1 (95% CI 0.8-1.7) Yasmin vs. LNG + Other COCs: 0.9 (95% 0.7-1.2)</p> <p>Hazard Ratios (Adjusted) (for age, BMI, duration of current use, VTE history) Yasmin vs. LNG: 1.1 (95% CI 0.8-1.7) Yasmin vs. LNG + Other COCs: 0.8 (95% CI 0.6-1.1)</p>

INTERPRETATION / Authors' Overall Conclusion	
Risk of VTE in Yasmin users is similar to those associated with the use of other OCs.	
KEY FACTOR	APPROACH
Duration of use/ Pattern of use	Groups stratified based specifically on lifetime history of use, duration of use, and pattern of use
Attrition of susceptibles/ Healthy user effect	Analysis by groups based on self-reported history of prior use, including first-time ever use cohort
Prescription bias	Key risk factors ascertained by questionnaire at baseline and updated every 6 months / Analyses adjusted for risk factors
Validity of diagnosis For VTE	Medical records review / Adjudication by 3 exposure-blinded experts

Strengths:

- Community-based observational study
- Ascertainment of events through a self-reported questionnaire administered every six months (during EURAS portion of study) and every twelve months (during LASS portion of study), documenting exposure and AEs
- Adjusted for predefined confounding factors: age, BMI, history (personal and family) of VTE
- Separate and pre-planned subanalyses based on duration and pattern of use, including first-time ever use; the time-dependent decline of the VTE incidence was similar for all OCs.
- VTE cases confirmed through clinical records review, and adjudication was done by 3 exposure-blinded experts
- Loss to follow-up was minimal (less than 3%)
- Search of governmental records for deaths to ensure all events were captured. (Multi-step algorithm for patient follow-up)

Limitations:

- The active surveillance process with prompted recall around events compatible with VTE may have driven an increased awareness of symptoms and signs of VTE and reporting. Media attention about the potential increased risk of VTE with Yasmin may have led to a referral/diagnostic bias, which would have increased the apparent risk of VTE to the detriment of Yasmin. The rate of confirmed diagnosis for VTE was lower among women using Yasmin compared to COCs, supporting this potential bias. (From final study report.)
- Diagnosis of VTE was based on local clinical standards, without a pre-specified diagnostic algorithm. Some diagnostic methods for VTE (eg, D-dimer) are known to be poorly reliable. This may have introduced a non-differential classification bias (validation of diagnosis) that may have reduced the likelihood of finding a difference between the groups observed.
- Inclusion in study required patient consent

Comment: Subanalyses were done for the following:

Switcher-starter analysis: The impact of ‘duration of current OC use’ was analyzed in detail for an interim report presented to the FDA and other regulatory agencies. This information applies to all COCs studied, and the wording below has been integrated to the YAZ label (currently pending inclusion in all of the sponsor’s COC labeling):

Interim data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.

As stated above, the study came to the conclusion that starting COC for the first time ever, or recurrent COC use after an intake break of at least four weeks, increased the VTE risk during the first 6 months following treatment initiation after which the risk remained fairly stable over time. The highest risk was seen, in particular, during the initial three months of treatment. For those COC users who switched preparations without an intake break of at least one treatment cycle (4 weeks), the VTE risk after the start of the new preparation intake was not statistically significantly higher than the risk associated with long term therapy. This analysis was repeated with the final data set for the final study report; the results were confirmed without exception.

0.03 mg EE/LNG only: A total of 35 VTEs were observed in the 30 mcg EE/LNG sub-cohort and 56 VTEs in the Yasmin cohort. This corresponds to an incidence of 10.9/10,000 WY for the LNG sub-cohort and 10.7/10,000 WY for the Yasmin cohort. The Cox regression analysis yielded a crude HR for Yasmin vs. LNG/30 mcg EE of 1.0 (95% CI: 0.7–1.5) and an adjusted HR of 1.0 (95% CI: 0.6–1.5).

“Idiopathic cases only”: For this analysis VTE cases with acute risk factors (such as pregnancy, delivery, trauma, immobilization, long-haul travel, surgery, and chemotherapy) were excluded. Overall, 100 out of 306 (32.7%) were associated with acute risk factors. The analysis was based on 216,038 WY of exposure and 206 confirmed “idiopathic” VTE cases. The Incidence Rates for Yasmin, LNG and other progestins were 8.2 (95% CI, 6.0-11.1), 7.8 (95% CI, 5.7-10.5) and 9.1 (95% CI, 7.4-11.1), respectively. Crude hazard ratios for DRSP vs. LNG and DRSP vs. other progestins were 1.0 (95% CI, 0.7-1.6) and 0.9 (95% CI, 0.6-1.3). After adjusting for age, BMI, duration of use, and family history of VTE, the corresponding adjusted hazard ratios were 1.0 (95% CI, 0.7-1.6) and 0.8 (95% CI, 0.6-1.2), respectively. Overall, the results on “idiopathic VTE” do not indicate a higher risk for the Yasmin cohort compared to the two other OC cohorts.

The LASS study adds five years of observation to the large cohort from the EURAS study. Overall the combined EURAS/LASS study cohort provides an unprecedented 10 years of prospectively collected data for a total of 318,784 WY of observation and 216,038 WY of OC exposure. This is noteworthy on two levels. On the one hand, it provides long-term

follow-up on users of COCs, with overall reassuring results. On the other hand, it provides extensive insights into the events associated with multiple episodes of starting or restarting a given COC, or switching between COCs, over a 10-year period. The data from EURAS/LASS are just now being disseminated and will contribute for years to come to the overall understanding of the benefit-risk profile of COCs.

4.7.1.3.2 Data on ATE

Table 4-6: Structured Summary of Study Design as Reported by the Authors for ATE - LASS

LASS, Dinger et al., unpublished / ATE DATA	
METHOD – As Described in VTE section above	
ASSIGNMENT	
Baseline exclusion criteria	Clinicians chose COC use based on their clinical judgment. No other specific inclusion or exclusion criteria were applied.
Assessment of COC use	As described in VTE section above
Comparator	As described in VTE section above
Method to address confounding	Risk factors ascertained via patient questionnaire. Adjustment in a regression model for predefined confounding variables: age, BMI, smoking, hypertension and family history of fatal ATE
ASSESSMENT	
ATE Definition	See EURAS study Section 4.7.1.2.2
ATE Validation Process	see EURAS study Section 4.7.1.2.2

Results:

For the combined EURAS and LASS database covering up to 10 years, there were 84 confirmed ATEs (17 AMIs, 46 strokes, 15 TIAs and 6 complete thromboses of peripheral or intestinal arteries)

Yasmin cohort: 7 events (incidence: 1.3 ATE/10,000 WY)

LNG cohort: 22 events (incidence: 3.8 ATE/10,000 WY)

Other OCs cohort: 34 events (incidence: 3.2 ATE/10,000 WY)

Non-oral hormonal contraceptives (NOHC) cohort: 4 events (incidence: 2.6 ATE/10,000 WY)

No use cohort: 17 events (incidence: 1.9 ATE/10,000 WY)

Cox regression analysis yielded adjusted (for adjusted for age, BMI, smoking, hypertension and a family history of fatal ATE) hazard ratios of 0.4 (95% CI, 0.2-0.9), 0.4 (95% CI, 0.2-0.9), and 0.4 (95% CI, 0.2-0.8) for Yasmin versus LNG, Yasmin versus Other OCs and Yasmin vs. all other OCs (incl. LNG), respectively. All three comparisons showed statistically significant differences between Yasmin and the comparator cohorts. (Table 4-7)

Table 4-7 Adjusted Hazard Ratios (HR) and Confidence Limits for ATE

	Yasmin versus					
	LNG-containing OCs		Other OCs		LNG & Other OCs	
	HR	95% CI	HR	95% CI	HR	95% CI
ATE	0.4	0.2 – 0.9	0.4	0.2 – 0.9	0.4	0.2 – 0.8

Numbers are from the Dinger 2007 publication.

Fatal cardiovascular outcomes were also ascertained in the LASS study (Table 4-8 below). Cardiovascular diseases were the leading cause for death among the non-cancer cases (0.5 cases/10,000 WY). The Yasmin cohort showed lower cardiovascular and total mortality compared to the other OC cohorts as well as the ‘no use’ cohort, but the study was not sufficiently powered to exclude chance as a likely explanation of the finding. Overall, these results yield no indication of an increased mortality that might be associated with Yasmin use.

Table 4-8: Fatal Outcomes: Number and Mortality Rates per Cohort

All Deaths	Total		Yasmin		LNG		Other OCs		NOHC		No use[#]	
	N	per 10 ⁴ WY*	N	per 10 ⁴ WY*	N	per 10 ⁴ WY*	N	per 10 ⁴ WY*	N	per 10 ⁴ WY*	N	per 10 ⁴ WY*
(95% CI*)	74	2.3 (1.8-2.9)	7	1.3 (0.5-2.8)	13	2.3 (1.2-3.9)	19	1.8 (1.1-2.8)	2	1.3 (0.2-4.8)	33	3.8 (2.6-5.3)

[#] no OC/NOHC use for at least 3 months before the fatal outcome

* CI = confidence interval

Also included in the analyses linked to ATE was an analysis relative to the use of anti-hypertensive treatments. A total of 2,284 (3.9%) study participants initiated antihypertensive treatment after study entry resulting in the following therapy initiation rates: Yasmin, 56.0/10,000 WY (95% CI 49.8-62.8); LNG, 81.7/10,000 WY (95% CI 74.5-89.4); Other OCs, 67.9/10,000 WY (95% CI 63.0-73.0); and ‘No use’ 76.2/10,000 WY (95% CI 70.5-82.1). These results suggest that less antihypertensive therapy was initiated in the Yasmin user cohort compared to the other cohorts. The absolute differences between Yasmin and the other OC cohorts were even more pronounced among users who had untreated hypertension at baseline. All analyses were statistically robust (p<0.001).

Interpretation / Authors' Overall Conclusion:

These results suggest that the risk of adverse cardiovascular outcomes for Yasmin use are not higher than the venous risks associated with the use of LNG-containing OCs or Other OCs, while the arterial risk appears to be lower.

Strengths: (retained items from prior sections pertaining to VTE are italicized)

- *Community-based observational study*
- *Ascertainment of events through a self-reported questionnaire administered every six months (during EURAS portion of study) and every twelve months (during LASS portion of study), documenting exposure and AEs*
- Adjusted for predefined confounding factors: age, BMI, smoking, hypertension and a family history of fatal ATE
- ATE cases confirmed through clinical records review
- *Loss to follow-up was minimal (less than 3%)*
- *Search of governmental records for deaths to ensure all events were captured. (Multi-step algorithm for patient follow-up)*

Limitations: (retained items from prior sections pertaining to VTE are italicized)

- *The active surveillance process with prompted recall around events compatible with ATE may have driven an increased awareness of symptoms and signs of ATE and reporting*
- *Diagnosis of ATE was based on local clinical standards, without a pre-specified diagnostic algorithm. This may have introduced a non-differential classification bias (validation of diagnosis) that may have reduced the likelihood of finding a difference between the groups observed.*
- *Inclusion in study required patient consent*

One critically important consideration in assessing the LASS study is that it was designed specifically to analyze rare events (incidence rate < 1 per 1,000 WY and > 1 per 10,000 WY). At study start it was expected that more than 300,000 documented women-years of observation would be captured during follow-up. Under the assumption that the true incidence rates of the outcomes of interest, in particular VTE and ATE, were not different from each other, exposure in the LASS study would be sufficient to exclude at least a two-fold risk in the DRSP cohort. Thus, under the assumption that the hazard ratios of ATEs or deaths/hospitalizations due to cardiovascular events would be 50% lower in the Yasmin cohort, exposure accumulated through LASS would be sufficient to show a statistically significant difference between the cohorts ($\alpha = 0.05$; $\beta = 0.2$).

Given the fact that the antihypertensive properties of DRSP/estrogen combinations have been proven in several randomized clinical trials, the LASS findings are plausible. These data strongly suggest that Yasmin users with pre-hypertension and hypertension less frequently need treatment for high blood pressure. These results might partially explain the lower risk of ATE found in this study.

Overall conclusions for LASS:

Overall the LASS study provides further support that the risk of adverse cardiovascular outcomes does not differ materially from the risks associated with the use of LNG-containing OCs or Other OCs. For ATE, the risk was lower with Yasmin than for comparators. For VTE, the risk with Yasmin use was similar to the use of LNG-containing OCs or Other OCs.

4.7.1.4 MEGA study (VanHylckama Vlieg A et al. 2009)

Information on the VanHylckama Vlieg A et al. was initially submitted to the FDA in October 2009 as part of the response to the 2009 BMJ publications. Details are provided in [Section 10.1 \(Appendix 1\)](#).

Table 4-9: Structured Summary of Study Design as Reported by the Authors – MEGA Study

MEGA Study, van Hylckama Vlieg et al 2009	
METHOD	
Objective	Overall objective of MEGA database: To explore the potential relationship between a range of putative risk factors and VTE; these included factors such as trauma and smoking. Of note, this study was not designed to study COCs. Objective of current study: To assess the thrombotic risk associated with OC use with a focus on dose of estrogen and type of progestogen of OCs available in the Netherlands.
Study Design	Observational population-based case-control study
Geography	Netherlands
Time Period	March 1999 – September 2004
Population / Source of Data	Data obtained from the MEGA study (multiple environmental and genetic assessment of risk factors for venous thrombosis study), a case control study of risk factors for VTE Cohort: 6257 women with VTE, < 70 years old (analysis restricted to women ages 18-50). Cases: first objective diagnosed episode of VTE Controls: Female partners of patients from the same VTE clinics, age 18 to 70 (40.5% of controls), matched by age Additional controls recruited by random digit dialing within the geographical inclusion area of the patients (59.5% of controls) Questionnaires mailed to subjects (cases and controls) requesting participation
Sample size	Cases: 1,524 / Yasmin: 19 LNG-COC: 485 Controls: 1,760 / Yasmin: 14 LNG-COC: 373

ASSIGNMENT	
Baseline exclusion criteria	Severe psychiatric problems, inability to speak Dutch, women who were postmenopausal, pregnant, or within 4 weeks postpartum at the time of the thrombotic event or index date and women using hormonal intrauterine contraception or depot contraceptive
Assessment of COC use	Questionnaire completed by subjects For 1,005 (66%) cases and 533 (30%) controls, information on duration of COC use on the index date was available.
Comparator	LNG COC
Method to address confounding	Statistical adjustment for age, date of inclusion (divided in periods of 6 calendar months), dose of estrogen, family history of VTE, BMI, smoking

ASSESSMENT	
VTE Definition	Notation of VTE in MEGA database Did not include fatal cases.
VTE Validation Process	Information on diagnostic procedure from hospital records and general practitioners. DVT confirmed by Doppler ultrasonography. PE confirmed by ventilation perfusion scan, spiral computed tomography, or angiogram. No treatment blinded reviewer.

RESULTS
<p>Risk of VTE compared to non-use (OR adjusted for age and period of inclusion)</p> <p>Yasmin: 6.3 (95% CI 2.9-13.7)</p> <p>LNG COCs: 3.6 (95% CI 2.9-4.6)</p> <p>Odds ratio for Yasmin vs LNG COCs: 1.7 (95% CI 0.7-3.9)</p>
INTERPRETATION - Author's overall conclusion
Our results clearly show that the safest option in regard to risk of VTE is an OC containing LNG combined with a low dose of estrogen.

KEY FACTOR	APPROACH
Duration of use/ Pattern of use	Questionnaire / Partial data on 60% of cases and 30% of controls
Attrition of susceptibles/ Healthy user effect	Key risk factors ascertained by questionnaire / Analyses adjusted for BMI and smoking. No adjustment made for family history
Prescription bias	Key risk factors ascertained by self-administered questionnaire / Analyses adjusted for BMI and smoking. No adjustment made for family history
Validity of diagnosis For VTE	Medical records as source to identify cases

Strengths:

- Cases were diagnosed in hospitals and clinics specialized in anticoagulation. Diagnostic methods encompassed up-to-date approaches, including Doppler studies, spiral CT and/or angiography.
- Several confounding factors were assessed through questionnaire: age, family history of VTE, BMI, and smoking. Analysis adjusted for smoking and BMI.

Limitations:

- Improper control group; nearly half of the group consisted of women who were domestic partners of men diagnosed with VTE in the participating centers and the other half were recruited in the general population, through random digit dialing. Only the latter group is representative of Dutch women at risk of VTE. The two sets of controls were merged into one control group for analysis purposes. No explanation provided for improper control group.
- Subjects in a coagulation clinic may have been differentially referred and represent a different subpopulation than the overall VTE population
- Very few Yasmin cases – reported difference is not statistically significant (95% CI 0.7 – 3.9)
- Despite use of questionnaire, duration of use information missing on large number of subjects (34% of cases and 70% of controls); therefore adjustment for this factor was inadequate
- Lay and professional media may have driven increased awareness of the risk of VTE with Yasmin, and led to a referral/diagnostic bias (which would have increased the apparent risk of VTE to the detriment of Yasmin)
- Family history information available (26.4% of thrombosis patients, 14.3% of controls with positive family history) and this information was used to run a subanalysis restricted to subjects without a family history of VTE, however, information on family history not incorporated into the overall analysis as a potential confounding variable
- Cases required to recall type of COC used in past, while control subjects reported currently used COC, thus potentially introducing recall bias
- Does not account for fatal VTE (potential for Neyman's bias).

The sponsor has two major concerns about the conclusions proposed by the authors of this study. First, the selection of the controls (ie, female partners of males with VTE) is highly unorthodox. This alone challenges the reliability of the findings for the entire study. Secondly, the reported results are consistent with chance. Yasmin was not associated with a statistically significant increase in VTE risk. The reported odds ratio of 1.7 (95% CI: 0.7-3.9) clearly overlaps 1.0 and thus is consistent with chance.

4.7.1.5 Danish study (Lidegaard et al. 2009)

Information on the Lidegaard et al. 2009 publication was initially submitted to the FDA in October 2009 as part of the response to the 2009 BMJ publications. Details are provided in [Section 10.1 \(Appendix 1\)](#).

Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009; 339: b2890 ([Lidegaard et al., 2009](#))

Table 4-10: Structural Summary of Study Design as Reported by the Authors – Danish Study

Danish Study, Lidegaard et al. 2009	
METHOD	
Objective	Assess the risk of VTE in current users of different types of hormonal contraception, focusing on duration of use, regimen (COCs vs. progestogen only pills), and the effect of estrogen dose, type of progestogen, and route of administration.
Study Design	Observational population-based cohort study
Geography	Denmark
Time Period	1995-2005
Population / Source of Data	Integrated data from Danish National Registry of Medicinal Products, National Registry of Patients, Statistics Denmark, Central Person Registry. Information includes: prescribed drugs, discharge diagnoses, surgical codes, births, abortions, length of schooling. Cohort included all non-pregnant women age 15 to 49 with no previous cancer or cardiovascular disease diagnosis. Cases: first time venous thrombotic events among current users of hormonal contraception
Sample size	total 10,447,373 WY Yasmin: (n not specified) 131,541 WY LNG-COCs (0.02-0.05 mg EE): (n not specified) 411,099 WY (see Ref Table 2 for full breakdown of all COCs studied) Cases: 2045/ Yasmin 103, LNG (0.02-0.05 mg EE) 201

ASSIGNMENT	
Baseline exclusion criteria	Malignant disease, cardiovascular event, pregnancy
Assessment of COC use	<p>Current use: Based on valid prescription in Registry for COCs of interest at the time of hospital admission</p> <p>Previous use: Any previous recorded use in the Registry during the study period</p> <p>Never use: No recorded prescription in the Registry for hormonal contraception during the study period</p> <p>Length of use: sum of valid prescriptions in the Registry, with periods of non-use subtracted if they occurred between periods of use</p> <ul style="list-style-type: none"> Length of COC use in current users: <1 year, 1-4 years, or >4 years
Comparator	<p>1. Non-use of COC</p> <p>2. LNG-containing COCs,</p> <p>In addition: COCs containing Norethisterone, NGM, gestodene, DSG, cyproterone</p>
Method to address confounding	<p>Adjusted analyses as follows:</p> <p>Educational level was categorized into four groups: primary school only, secondary school only, any school with three or four years of further education, and secondary school with five or six years of further education; age</p> <ul style="list-style-type: none"> Found to be a significant confounder and was included in the analysis <p>Potential confounders (eg, increased lipids, heart disease, hypertension) based on prescription data for the corresponding condition</p> <ul style="list-style-type: none"> Influenced risk estimates by less than 5%, and were consequently excluded

ASSESSMENT	
VTE Definition	<p>Based on ICD 10 codes during the study period</p> <p>Unclear as to whether fatal cases were included</p>
VTE Validation Process	None specified

MAIN RESULTS

Crude VTE Incidence Rates (n)

Yasmin 7.83/10,000 WY (103) / LNG-COC (0.02-0.04 mg EE) 5.47/10,000 WY (201)

(See Ref Tables 1–3 for the results on all studied COCs)

Adjusted Rate Ratios (Compared to non-use of COC) – Overall

Yasmin: 4.00 (95% CI 3.26 to 4.91)*

LNG-COCs (0.02-0.04 mg): 2.02 (95% CI 1.75 to 2.34)*

- Adjusted for age, calendar year, and education level

Additional subanalyses performed based on duration of use

Comparing Yasmin to LNG-COC (0.02-0.04 mg EE) – Overall

Rate Ratio: 1.64 (1.27 to 2.10)

INTERPRETATION - Authors' overall conclusion

Risk of VTE in current COC users decreases with duration of use and decreasing estrogen dose. For the same dose of estrogen and length of use, COCs containing DSG, gestodene, or DRSP were associated with a significantly higher rate of VTE than COC users with LNG.

KEY FACTOR	APPROACH
Duration of use/ Pattern of use	Duration of use based on sum of valid prescriptions in the Registry, with periods of non-use subtracted if they occurred between periods of use / No separate analysis for pattern of use
Attrition of susceptibles/ Healthy user effect	Education and prescription data as surrogates for potential risk factors / Baseline exclusion of known malignancy and cardiovascular events including prior VTEs
Prescription bias	Education and prescription data as surrogates for potential drivers of Prescription bias. No data on BMI or family history of VTE available
Validity of diagnosis For VTE	Database entry only / No chart review / No adjudication process. Known inconsistencies in the database exist.

Strengths:

- Exposed subjects identified without prior knowledge of outcome (VTE) (prospectively assembled cohort)
- Large size
- Population-based design using a closed population
- Several potential confounders were monitored: age, year of data collection and level of education (though the latter is proposed as a surrogate for other well-established confounding biases)

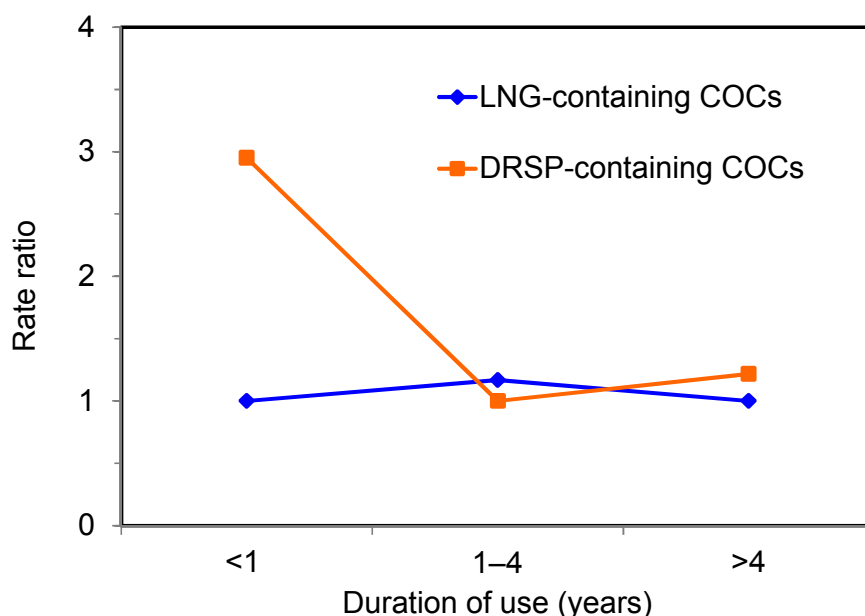
Limitations:

- Misclassification of duration of use, especially in the LNG-COC user cohort. This is most evident by the absence of a demonstrated increase of VTE during the first year of use among LNG-COC users, in contrast to all other COCs reported on in the study.

- The estimated duration of use was also invalid because it was calculated by adding all periods of use and subtracting periods of non-use, thus not accounting appropriately for the increased risk of VTE upon starting/re-starting a COC.
- Information on BMI and personal/family history of VTE not available. Other potential confounders (eg, hypertension) based only on prescription data
- There was no validation process for VTE cases
- No information available on COC usage prior to 1995
- Cases were identified in the registries only on the basis of hospital admission. Despite the authors' claim of only 10% misclassification of diagnosis, other investigators have reported nearly 40% of diagnoses could not be confirmed, from the same set of databases (Severensen)
- Excludes fatal VTE which may introduce Neyman's bias. Cases in the study may not be representative of VTE cases in Denmark, since the most severe cases are excluded.

The sponsor finds three major issues with this study which challenge the validity of the conclusions. First is the failure to account appropriately for duration and pattern of use, especially for the reference COCs, those containing LNG. The failure to detect an increased risk of VTE during the first year of use for LNG-COC users only, provides strong support for this concern ([Figure 4-4](#)). A second major concern is inadequate covariates – no consideration of BMI or personal family history of VTE. Socio-economic status has not been validated as an adequate surrogate for these important covariates and it is extremely unlikely that socio-economic status, as captured in the study, could replace individual analysis of these factors. The third major concern is the lack of validation of VTE cases, which may create differential misclassification if there is underlying referral or diagnostic bias based on treatment. These three issues are fundamental flaws in the study.

Figure 4-4: Detection of Risk of VTE Among DRSP-Containing and LNG-Containing COCs in Lidegaard 2009



The sponsor's assessment is that the conclusions presented by the authors are unreliable, and that the comparison of the VTE risk between DRSP and LNG-containing OCs is not valid.

4.7.1.6 Lidegaard reanalysis ([Lidegaard et al., 2011a](#); [Lidegaard et al., 2011b](#))

The Lidegaard reanalysis final study report ([Lidegaard et al., 2011a](#)) was submitted to the FDA in April 2011

Upon review of the 2009 Lidegaard et al publication in the BMJ, the Medicines Evaluation Board (MEB) on behalf of the Pharmacovigilance Working Party (PhVWP) of the EMA requested a reanalysis of the data. Specifically, the reanalysis of the Danish National Registries was to be restricted to the time period from 2001 to 2005. The start point of 2001 was selected to coincide with the initial approval of Yasmin in Denmark in an attempt to better account for duration and pattern of use between LNG-containing COC users and Yasmin users, a major shortcoming of the 2009 publication. Because this study was initiated as a reanalysis of the 2009 publication, it is discussed here, instead of in chronological order.

The reanalysis by Prof. Lidegaard as Principal Investigator was overseen by a Steering Committee. At the request of the EMA, the sponsor provided the funding to conduct the reanalysis. The investigators provided a reanalysis report on 31 March 2011 which was submitted to the Health Authorities, and subsequently published a selection of the results of the reanalysis in October 2011, in the British Medical Journal ([Lidegaard et al., 2011b](#)).

Discussion of 2011 BMJ publication by Lidegaard et al

The following table lists the information as presented in the October 2011 BMJ publication. The publication is mainly based on the first and parts of the second analysis of the initial study report. In addition, the publication also reports limited data on DRSP-containing COCs with 0.02 mg EE (Yasminelle and YAZ) without further distinguishing by regimen (ie, 21 vs. 24 days). It should be noted that this additional analysis was not part of the original protocol for the Lidegaard reanalysis. It is highly unlikely that a significant number of YAZ users were included in the analysis as YAZ was launched in Denmark in October 2008 only. Overall exposure for this cohort is low: 23,059 WY (around 8% of the Yasmin exposure in the study) with 23 VTEs in the group of 0.02 mg EE/DRSP containing COCs.

Table 4-11: Structured Summary of Study Design as Reported by the Authors – Danish Reanalysis

Danish Reanalysis, Lidegaard et al. 2011	
METHOD	
Objective	Assess the risk of VTE from use of COCs according to progestogen type and estrogen dose.
Study Design	Observational population-based cohort study
Geography	Denmark
Time Period	2001-2009
Population / Source of Data	<p>Integrated data from Danish National Registry of Medicinal Products, National Registry of Patients, Statistics Denmark, Central Person Registry and National Cause of Death Registry. Information includes: filled prescriptions, discharge diagnoses, surgical codes, pregnancies, length of schooling, lethal events from VTE (until 2008).</p> <p>Cohort included all non-pregnant Danish women age 15 to 49 with no previous cancer diagnosis and history of thrombotic disease.</p> <p>Cases: first time venous thrombotic events among current users of hormonal contraception</p>
Sample size	<p>Total (including non-use) 8,010,290 WY (n= 1,296,120) Yasmin: (n not specified) 286,862 WY LNG-COCs (0.03-0.05 mg EE): (n not specified) 233,912 WY (see Ref Table 2 for full breakdown of all COCs studied)</p> <p>Cases (confirmed and unconfirmed): Total 4246 (including non-use) Yasmin 266, LNG (0.03-0.05 mg EE) 198</p>

ASSIGNMENT	
Baseline exclusion criteria	Malignant disease (gynecological, abdominal, organ, breast, hematological), VTE/ATE before study period, bilateral oophorectomy, hysterectomy, sterilization, pregnancy/postpartum, diagnosed coagulation disorders; use of ovarian stimulation drugs
Assessment of COC use	<p>Redeemed prescription information from the national registry of medicinal products.</p> <p>Start use: Use of COCs with no history of hormonal contraception before first prescription</p> <p>New use: Start use after a pause of at least 12 wks for any prescription of hormonal contraception</p> <p>Restarted use: OC use after a pause of 4-11 wks</p> <p>Switched use: Use of one OC followed by use of a different preparation within a pause of less than four wks</p> <p>Continuous use: same OC preparation with less than 4 weeks break</p> <p>Duration of use:</p> <p>For continuous, starting and new use: duration was calculated from the date of prescription until day of last redeemed prescription or event.</p> <p>For restarted use, from data of restart until the end date of last redeemed prescription or event.</p> <p>For switched use, duration was the sum of use before the switch and current use on new preparation.</p> <p>To account for use before the start of the study (left censoring bias) assessed OC use before study period back to 1995. These continuous users were allocated to appropriate length of use category.</p> <p>Length of use categories in current users: <3 months, 3-12 months, >1-4 years, or >4 years</p>
Comparator	<p>1. Non-use of COC</p> <p>2. LNG-containing COCs,</p> <p>In addition: COCs containing norethisterone, NGM, gestodene, DSG, cyproterone</p>
Method to address confounding	<p>Adjusted analyses as follows:</p> <ul style="list-style-type: none"> • Educational level (proxy for social class) was categorized into four groups: elementary school only, ongoing or completed high school education, high school and ongoing or ended middle education (3-4 years after high school), high school and ongoing or ended long education (5-6 years after high school); or unknown. • Calendar year (proxy for long-term confounding by BMI) • Age • Length of use

ASSESSMENT	
VTE Definition	<p>Based on ICD 10 codes</p> <p>Three categories presented:</p> <ol style="list-style-type: none"> 1. All cases 2. “Confirmed cases” : Anticoagulation treatment (based on national registry of medicinal products) for at least 4 weeks was considered “confirmed” case 3. Unconfirmed cases: All cases minus “confirmed cases”
VTE Validation Process	<p>200 cases (out of 4246) were randomly selected for validation using hospital charts and reviewed by two treatment-blinded clinicians.</p> <p>Validation based on presence of 2 out of 3 criteria:</p> <ul style="list-style-type: none"> • Clinical signs of VTE • Diagnostic confirmation (ultrasound, phlebography, CT, or scintigraphy) • At least four weeks of anticoagulation therapy <p>Out of 200 randomly selected cases, 148 cases (74%) were considered ‘validated’.</p>

MAIN RESULTS
<p>Crude VTE Incidence Rates (n) confirmed and unconfirmed</p> <p>Yasmin 9.3/10,000 WY (266)</p> <p>LNG-COC (0.03-0.04 mg EE)</p> <p> Phasic only 8.4/10,000 WY (89)</p> <p> All 7.5 / 10,000 WY (78)</p> <p>(See Ref Table 2 for the results on all studied COCs)</p> <p>Adjusted Relative Risk (Compared to non-use of COC)</p> <p>Yasmin: 4.47 (95% CI 3.91 to 5.11)*</p> <p>LNG-COC (0.03-0.04 mg EE)</p> <p> Phasic only 2.28 (95% CI 1.85 to 2.83)*</p> <p> All 2.19 (95% CI 1.74 to 2.75)*</p> <p>(See Ref Table 2 for results on all studied OCs)</p> <p>Additional subanalyses performed for confirmed/non-confirmed cases, age, calendar year, level of education and/or duration of use</p> <p><u>Adjusted Rate Ratio comparing Yasmin to LNG-COC (0.03-0.04 mg EE, all) – Overall</u></p> <p> Confirmed events only: 2.12 (95% CI 1.68 – 2.66)*</p> <p> Non-confirmed events only: 1.78 (95% CI 1.21 – 2.60)*</p> <p>(See Ref Table 4)</p> <p>*Adjusted for age, calendar year, and education level</p>

INTERPRETATION - Authors' overall conclusion	
After adjustment for length of use, users of OCs with DSG, gestodene, or DRSP were at least at twice the risk of VTE compared with users of OCs with LNG.	
KEY FACTOR	APPROACH
Duration of use/ Pattern of use	Duration of use based on defined categories, with users potentially having several episodes of use
Attrition of susceptibles/ Healthy user effect	Education as surrogate for potential risk factors / Calendar year as surrogate for BMI (No data on BMI or family history of VTE available), personal history of thrombotic events based on information in database / no information on use of OC before 1995/ Baseline exclusion of known malignancy and cardiovascular events / Retention of subjects who started continuous use before 2001 allocating them to the respective duration of use categories.
Prescription bias	Education and prescription data as surrogates for potential drivers of Prescription bias. No data on BMI or family history of VTE available
Validity of diagnosis For VTE	Confirmation of cases based on surrogate measures (anticoagulation treatment for 4 weeks) (approach not used in all calculations) / No complete chart review. Approximately 5% of randomly selected cases extracted for medical record review and validation

Strengths:

- Exposed subjects identified without prior knowledge of outcome (VTE) (prospectively assembled cohort).
- Large size
- Population-based design using a closed population
- Subjects classified according to duration of use, use definitions given

Limitations:

- Inclusion of subjects that started COC use before start of study in 2001, therefore not comparing similar cohorts (DRSP was marketed starting in 2001)
- Inconsistent duration of use effect compared to 2009 publication for all studied progestogens suggesting lack of robustness of exposure data.
- Information on BMI and family history of VTE not available. Personal history of thrombotic events based on available information in database since 1994.
- Identification of cases based on hospital admission diagnoses, confirmation of cases based on surrogate measure (anticoagulation).
- Incomplete clinical validation: medical charts review performed in a random sample of approximately 5% of all cases; of these, only 74% could be validated. Validation criteria do not require confirmation of diagnosis based on imaging procedure.
- Incidence rates not adjusted in accordance with validation results (this should have been done, especially since the confirmation rates seem to vary between drugs).

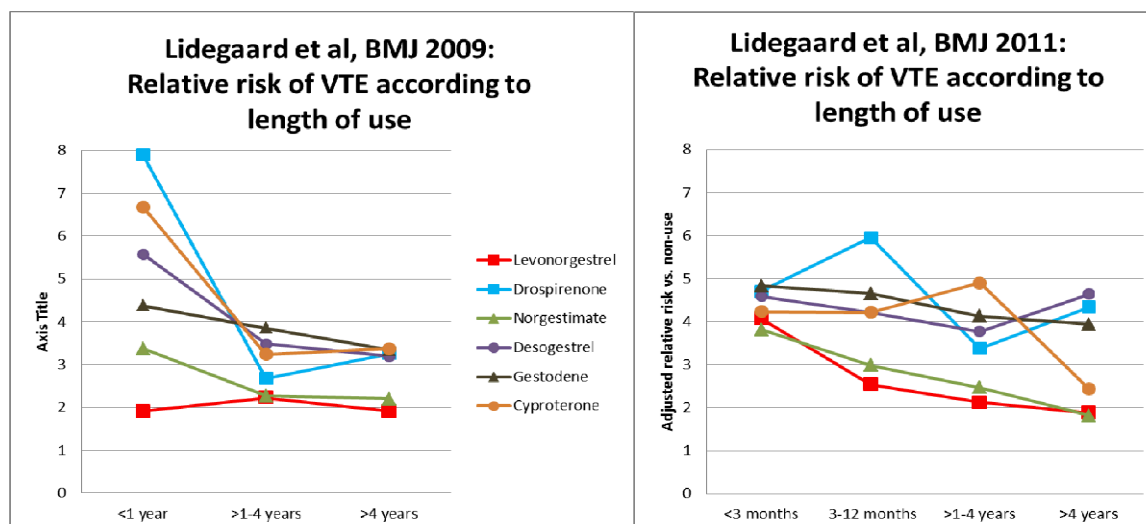
During the review of the 2009 Danish database study (Lidegaard et al), two major issues were identified which seriously challenged the validity of the conclusions:

1. The first was the failure to account appropriately for duration and pattern of use, especially for the reference COCs, those containing LNG. The failure to detect an increase risk of VTE during the first year of use, only among LNG-COC users provided strong support for this concern ([Figure 4-5](#)).
2. The second was the lack of validation of VTE cases.

These two issues point to fundamental flaws in the 2009 study. Ideally, for a reanalysis, the principal investigator would use the identical set of data and databases from the original study while addressing the above mentioned flaws. The reanalysis, however, uses the National Cause of Death Registry instead of the Central Person Registry. An additional 4 years of data is added as LNG exposure is reduced in the years after 2001 compared to the time period before that (ideally, the time period 2001 to 2005 should also have been reported in the 2011 BMJ publication). Of concern, the total number of VTE cases obtained from the Danish National Patient Registry is not expected to change when comparing the same time period for the same COC between the two analyses (years 2001 to 2005). In the 2009 publication, there were 103 Yasmin VTE cases; in the reanalysis, there are 128 cases (refer to appendix 3 of publication). No explanation is offered for this 25% increase in the number of VTEs; inconsistencies in this order of magnitude cast doubts on the reliability of data extraction.

Based on the relative risks according to duration of use (refer to table 6 of the publication for details) in the 2011 reanalysis it appears that the investigator addressed the duration of use and 'left truncation bias' for the LNG-COCs. As one would expect, in the reanalysis, users of LNG-containing COCs show a higher risk of VTE during the first year of use and lower rates thereafter (a pattern not present in the original 2009 analysis). Inexplicably, however, the higher risk in the first year for all other COCs demonstrated in the 2009 analysis now seems to have diminished, raising questions about potential misassignment in the duration of use (see [Figure 4-5](#) below).

Figure 4-5: Relative Risk of VTE According to Length of Use – Lidegaard BMJ 2009 and 2011



Additionally, while duration of use appears to be accounted for in the reanalysis, it cannot account for new (ie, first-time ever or starters in the 2011 BMJ publication) users. Yasmin was introduced to the Danish market in 2001. Multiple other studies have shown that when a COC is first introduced, it is prescribed to more first time users. Because the study period in this study begins in 2001, it is highly likely that even if duration of use is accounted for, the Yasmin group will contain more first-time users (as opposed to restarters) than the LNG-containing COCs which have been on the market for many years. With regard to the analysis of new users/starters (refer to Appendix 4 of the publication [Lidegaard et al. 2011b]) it should be noted that the start date for LNG users could be between 1995 and 2001 in contrast to DRSP which became available in 2001. It is not possible to compare the exposure in this particular subgroup between the cohorts between the 2011 and 2009 publication as it is not given.

The second concern related to the 2009 Lidegaard study was the validity of VTE diagnoses. In his 2009 paper, Lidegaard stated that previous validation of VTE diagnoses in the Danish National Registry of Patients found about 10% uncertain cases. Subsequent analysis of the Danish National Patient Registry by Severinson et al in 2010 (performed following the Danish cohort study “Diet, Cancer and Health”), however, found a misclassification rate for VTE of almost 40%.

Severinson et al (2010) found that out of the 1100 VTEs they investigated in their validation study of the Danish National Patient Registry, 454 of these diagnoses (41%) were given in the emergency room based on clinical suspicion only. These patients were then generally medicated (ie, received anticoagulants) and were admitted to the ward for definitive evaluation. Out of 418 patients admitted to the ward, 234 (56%) ultimately did not have a diagnosis of VTE. Severinson concluded that a VTE diagnosis based on the emergency room was not reliable. On the hospital wards, for DVT, the positive predictive value (PPV) of a diagnosis code for DVT for a woman was 63.2%; for a man, it was

77.2%, also indicating the presence of a potential referral bias for women ([Severinsen et al., 2010](#)).

In his 2011 reanalysis, Lidegaard addressed the issue of validity of diagnosis of VTE. His review found that 33% of cases designated as VTE in the database did not receive anticoagulation for 4 or more weeks. For his analyses, he designated these cases as “unconfirmed.” The percentage of unconfirmed cases varied by product and ranged from 44.6% for subjects not using hormonal contraception to 16.4% for women using DSG-containing products. In addition it has to be acknowledged that the accuracy of anticoagulation treatment information is highly uncertain in databases due to the fact that treatment is usually initiated in hospital but continued on an outpatient basis.

Lidegaard also attempted a separate validation of the VTE diagnoses within the database. A random sample of 200 cases was selected for blinded chart review; this represented approximately 5% of the VTE cases. A case was considered “validated” if it met 2 of 3 criteria: clinical signs of VTE; diagnostic confirmation by ultrasound, phlebography, CT, or scintigraphy and/or at least four weeks of anticoagulation therapy after the diagnosis. Utilizing this validation algorithm, it was possible for a case to be considered “validated” even if no objective testing by an imaging procedure was performed. Despite this nonrigorous approach, only 74% of cases in the database could be confirmed; considerably higher than the 90% he proposed in 2009. Given the fact Lidegaard demonstrated it was possible to link database information to actual medical records, blinded medical chart review utilizing a rigorous validation algorithm could have rectified this marked shortcoming. In both BMJ publications, it is evident that the Danish registries suffer from a considerable lack of validity regarding VTE diagnoses which has the potential to undermine the robustness of the results in particular for small increases in risk.

Validity of diagnosis becomes problematic if an invalid diagnosis is more likely to occur in one group over another. Neither of the Lidegaard studies ([Lidegaard et al., 2009](#); [Lidegaard et al., 2011b](#)) was able to control for preferential prescribing based on underlying patient characteristics (prescription bias). The EURAS trial, which followed patients from 2000 to 2005, found that in Europe, Yasmin was preferentially prescribed to women with higher risk for VTE (eg, higher weight). The EURAS study also found that while 18.2% of Yasmin users with possible VTE symptoms actually had a confirmed VTE, the percentage for LNG-containing COCs was 25.8%, demonstrating a referral bias existed. In addition, Lidegaard points to the “pill crisis” in Denmark in 2007 (similar to other pill scares which began in Europe in 1995) also raising the risk for referral bias.

The reanalysis addresses, at least in part, one of the two major shortcomings of the 2009 study as it categorized users according to duration of use. The 2011 results provide strong evidence that the results from the 2009 publication are invalid as the data for LNG, in particular, has changed considerably. Nevertheless, in the current reanalysis, there remain concerns about the manner in which the authors addressed duration of use. In the 2011 BMJ paper the expected pattern of higher event rates during the first year for LNG-containing COC users now is contrasted by the loss of a clear pattern for most of the other COCs studied. Regarding the other main deficiency of the initial publication, the lack of validation for cases of VTE through a review of all medical records is not addressed in the reanalysis. Additional data on the unreliability of VTE diagnoses in the database

generated by the authors simply serve to consolidate how significant of an issue this represents. These biases raise a serious question about the differential accuracy of a VTE diagnosis based on type of progestin.

In summary, the 2011 reanalysis of the Danish study provides solid evidence that the results from the 2009 publication are invalid. On its own merit, the 2011 reanalysis still suffers from significant methodologic limitations that make the results also invalid.

The complete reanalysis report contains more data than the subsequent publication. In order to allow for a complete presentation of the data, both the reanalysis report and the publication are also discussed below.

Summary of the reanalysis report ‘Oral contraception and venous thromboembolism – supplementary analyses of Danish Registry data’

The reanalysis report was shared with the European Health Authorities (who had initially requested it), the FDA, and other major regulatory bodies. Analyses were conducted for three sub-periods; 2001-2005, 2006 – May, 2007, as well as June 2007 through 2009.

The Principal Investigator presented a number of analyses outputs during the evaluation phase of the study results. In analysis 1, reflecting the Principal Investigator’s approach, the RR between COC with Yasmin and LNG was around 2.2, and between COC with Yasmin and DSG/gestodene around 1.1. In analysis 2 differential sub-periods were analyzed for confirmed events only, and detailed stratified analyses done according to OC-type, duration of use, and to education. The periods applied in analysis 2 were 2001-2006 and 2001-2009 with rate ratio estimates between COC with Yasmin and LNG were around 2.4 (1.7-3.6) and 2.3 (1.7-3.2), respectively. In Analysis 3, restricted to women with at least 12 weeks of pause in hormonal contraception before inclusion and restricted to the periods 2001-2005, 2001-2006 and 2001-2009, the relative risk between COC with DRSP and LNG for all VTE were (for the raw exposure string) 2.0 (1.3-3.2), 1.9 (1.3-2.7) and 1.7 (95% CI 1.3-2.3), respectively.

The Principal Investigator concluded that his study showed a 3-fold increased risk for confirmed VTE events in current users of COC with LNG, and a 6-7 times increased risk of VTE in users of COC with DSG, GSD, DRSP or cyproterone when compared with non-users with a rate ratio between the latter groups and the former group of about 2.

Sponsor’s Assessment: The final report contains three different datasets, the first one reflects the Principal Investigator’s approach to the analysis included in the report body, the second one is based on confirmed VTE cases and the third limits the exposure to starters and new users within the defined time period from 2001 onwards are presented in an appendix. Only the third analysis provides the data which are closest to those requested by the PhVWP.

It is crucial to note that the reanalysis provided by Prof. Lidegaard still includes long-term LNG users that started LNG use before 2001 (eg, users with continued COC use that was first recorded between start of collection of prescription data in Denmark in 1995 and start of the analysis period in 2001). Those subjects could enter the study being categorized as

start users of LNG. Consequently, all DRSP users could only start from 2001 onwards, whereas the LNG users (and all other progestin users) could have started between 1995 and 2001. The Steering Committee reiterated guidance to the Principal Investigator that the reanalysis should focus on the period after 2001 and in particular, that the main focus of the analysis should be the comparison of users after 12 weeks of no-use. This approach allows for a clearer exposure definition and VTE event allocation and provides a basis for a valid comparison of the user populations of interest. It is important to note that many of the tables presented in the report still contain LNG users before 2001. The analysis that comes closest to the requested analysis is provided in analysis 3.

One important finding is that the age adjustments lead to a marked change in RR, pointing to the fact that there is most likely a considerable age difference between the populations. A total of 74.2 % DRSP exposure was in women 15-29 years of age whereas the majority of LNG use (57.4%) was in women 30-49 years of age. This important age difference might account for the notable differences between the crude rate ratios overall (generally not shown by the Principal Investigator in tables, but added in italics to below table) and the adjusted rate ratios (see [Table 4-12](#) below). The difference between crude and age-adjusted RR for the complete cohort is even larger, at 0.6 (Crude RR 1.13, Age-Adjusted 1.73). It is unlikely that age adjustment alone can account appropriately for differences across these user populations.

Table 4-12: From Final Study Report - Table 10 from Analysis 3 Modified by Sponsor to Include Crude RRs (*in italics*)

Only women with at least 12 weeks without OC use before start												
2001-2009 ^a	Women years		VTE all		VTE confirm		<i>All VTEs Crude RR</i>	<i>Confirmed VTEs only Crude RR</i>	All RR	Conf RR*	95% CI conf	
	n	N	n	N	N	n					Low	High
Start use only												
DRSP/LNG	67.199	9.630	61 ^b	10 ^c	46	8	0.87	0.82	1.22	1.18	0.55	2.52
Start + new use												
DRSP/LNG	145.587	48.520	139	47	101	32	0.99	1.05	1.70	1.85	1.24	2.77
Start + new + re-started use												
DRSP/LNG	199.925	67.375	183	60	131	43	1.03	1.03	1.72	1.71	1.20	2.45
All categories												
DRSP/LNG	243.176	83.792	219	70	160	49	1.08	1.13	1.67	1.73	1.24	2.40

^a Labeled 2001 -2005 in Table 10, report body, page 30

^b N = 59 in Table 10, report body, page 30

^c N = 37 in Table 10, report body, page 30

The data about the subgroup of COC users who had no recorded use of any COC between 1995 and 2000 are presented below. In this analysis, the rate ratio estimates between users of COC with DRSP versus LNG ranged from 0.5 to 1.9 for different duration categories, with an overall rate ratio of 1.0

Table 4-13: Excerpt from Table 16, Analysis 3; Restricted to Starters and New Users of LNG- and DRSP-Containing OCs; Columns in *italics* (IR, RRcrude (1), RRcrude (2), RR^{*}) were added by the sponsor**

Restricted to starters and new users 2001-2009										
RR estimated on confirmed events, adjusted for age, no OC 1995-2000										
OC type	Duration	WY	VTE conf.	IR ^b	OC use vs. No use				DRSP vs. LNG	
					RRcrude (1)	RR ^a	Low	High	RRcrude (2)	RR ^c
No use		2,841,565	640	2.3	1	1	ref	ref	n/a	n/a
LNG	All	13,546	11	8.1	3.6	8.2	4.5	15.0	1	1
DRSP	All	91,990	60	6.5	2.9	8.2	6.1	11.0	0.8	1.0

^a Mantel Haenzel estimates adjusted for age

^b Incidence Rate (VTE/10.000 VTE)

^c Approximated by RR*DRSP vs. No use/RR*LNG vs. No use

The analysis requires a number of working assumptions in order to be able to account for lack of exact information in the database, such as exposure definitions and the allocation of events to exposure. These assumptions lead to a high variability of point estimates/rate ratios (up to 3-fold) without any consistent pattern (see highlights in [Table 4-14](#) below).

Table 4-14: Impact of Different Assumptions on Rate Ratio Calculations – Table 14 from Analysis 3, reanalysis report

COC with LNG	<1 year			1-4 years			>4 years		
	RR	Low	High	RR	Low	High	RR	Low	High
No new criteria in effect, 1995-2005 ¹	2.04	1.40	2.97	2.09	1.66	2.63	1.97	1.61	2.4
No new criteria in effect, 2001-2005 ¹	5.23	2.17	12.60	2.25	1.30	3.90	1.89	1.49	2.41
Extension of use with 4 weeks ²	6.07	2.72	13.56	2.27	1.31	3.92	2.07	1.64	2.61
Exclusion of 4 weeks after switch ³	6.19	2.77	13.83	2.29	1.32	3.96	2.06	1.63	2.61
Change in duration of use definition ⁴	3.15	2.24	4.45	1.80	1.22	2.66	1.95	1.39	2.74
Restriction to confirmed events ⁵	4.25	2.86	6.31	2.30	1.46	3.64	2.57	1.75	3.78
Introduction of wash out period ⁶	4.32	2.54	7.37	2.26	0.93	5.46	-	-	-
COC with DRSP	<1 year			1-4 years			>4 years		
	RR	Low	High	RR	Low	High	RR	Low	High
No criteria in effect ¹	8.46	6.03	11.87	3.27	2.35	4.55	2.97	2.16	4.1
Extension of use with 4 weeks ²	9.76	7.07	13.47	3.55	2.57	4.90	3.08	2.24	4.24
Exclusion of 4 weeks after switch ³	10.04	7.28	13.86	3.62	2.62	5.01	3.14	2.28	4.33
Change in duration of use definition ⁴	5.57	4.39	7.07	3.26	2.33	4.56	2.43	1.15	5.13
Restriction to confirmed events ⁵	7.41	5.54	9.92	5.40	3.73	7.81	3.84	1.71	8.65
Same but period 2001-2009	7.25	5.85	8.98	4.90	3.75	6.40	5.76	3.87	8.56
Introduction of wash out period ⁶	7.52	5.56	10.17	5.12	3.31	7.91	-	-	-
Same but period 2001-2009	7.23	5.79	9.01	4.66	3.47	6.27	5.84	3.19	10.68

1) Baseline criteria: Period 2001-2005, Duration defined as in BMJ 2009 paper, no extension of strings, no exclusions after switch, all events included, no wash out period.

2) Extension of current use with four weeks after expire of prescription

3) Exclusion of risk time and VTE events during first four weeks after switch

4) Change from definition in BMJ paper to definition in EMA analysis

5) Only confirmed events included

6) Restriction to starters and new users = at least 12 weeks of non use before current use

The reanalysis sheds new light on the shortcomings of the 2009 publication. Several issues that were to be addressed through the process of the reanalysis were either not addressed or not presented in the 2011 publication. On its own merit, the 2011 reanalysis still suffers from significant methodologic limitations, such as inappropriate allocation for duration and pattern of use and lack of validation for VTE cases that make the results of the reanalysis also invalid.

4.7.1.7 German case-control study (Dinger et al., 2010)

Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. J Fam Plann Reprod Health Care 2010; 36(3): 123–129; (Dinger et al., 2010)

The German case-control study was commissioned by the sponsor in Germany as a postmarketing study. The study was funded by the sponsor and conducted independently by ZEG. The study was specifically designed to investigate whether a 2 mg dienogest/0.03 mg EE COC (Valette – available in Europe only) is associated with a higher risk of VTE than other low-dose (0.03 mg EE or less) COCs, particularly LNG-containing COCs. The comparison of the risk of VTE with Yasmin versus low-dose LNG-containing COCs was a secondary endpoint pre-specified in the protocol.

Table 4-15: Structured Summary of Study Design as Reported by the Authors – German Case Control Study

German Case Control, Dinger et al. 2010	
METHOD	
Objectives	<p>To clarify whether the use of the OC containing 2 mg dienogest/0.03 mg ethinyl estradiol (DNG/EE) is associated with a higher risk of VTE than the use of other combined oral low-dose contraceptives (ie, containing ≤ 0.03 mg EE), particularly OCs containing LNG.</p> <p>Secondary objective: To investigate the VTE risk associated with Yasmin in comparison to low-dose LNG/EE.</p>
Study Design	Observational case-control study – retrospective
Geography	Germany
Time Period	January 2002 to February 2008
Population / Source of Data	<p>Community based study centers (including outpatient offices from the primary care sector and specialized diagnostic centers from all federal states of Germany)</p> <p>Cases: Eligible cases were women, aged 15–49 years, with a clinical diagnosis of VTE.</p> <p>Controls: Each case was matched with four community-based controls according to year of birth and area of residence.</p>
Sample size	<p>Cases: 680 / Yasmin: 25, LNG-COCs: 60</p> <p>Controls: 2,720 / Yasmin: 84, LNG-COCs: 197</p>

ASSIGNMENT	
Baseline exclusion criteria	Women without informed consent and/or who were unable to communicate in German.
Process	VTE cases identified by treating physicians for potential participation as cases. Patients were asked by their physicians to participate in the study, and completed a questionnaire on personal characteristics, symptoms and signs of VTE, and potential risk factors for VTE. The medical records for all eligible cases were abstracted by the reporting physician using a questionnaire, focusing on results of diagnostic procedures and therapeutic measures. The controls were asked to complete a similar questionnaire.
Assessment of COC use	Questionnaire completed by subject
Comparator	Low-dose LNG/EE COC preparations
Method to address confounding	Statistical adjustment for personal history of VTE, family history of VTE, BMI, duration of COC use, parity, educational level, chronic disease, concomitant medication and smoking

ASSESSMENT	
VTE Definition	Clinical diagnosis of VTE (DVT or PE) confirmed by imaging procedures or clinical examination plus a positive result from a less specific diagnostic test and/or specific anticoagulation treatment. Did not include fatal cases
VTE Validation Process	Medical chart review; Adjudication by 3 treatment-blinded physicians. (VTE was classified as definite if at least one of the adjudicators classified it as confirmed)

RESULTS
No event rate estimate provided in publication. Odds ratio for VTE for Yasmin vs. LNG-COC users: Crude: 1.0 (95% CI 0.6-1.6) Adjusted: 1.0 (95% CI 0.5-1.8) (Adjusted for personal history of VTE, family history of VTE, BMI, duration of COC use, parity, educational level, chronic disease, concomitant medication and smoking)

INTERPRETATION - Author's overall conclusion	
This study did not find any evidence of increased VTE risk among users of DRSP/EE (Yasmin) compared with users of low-dose LNG/EE COC preparations.	
Key Factor	Approach
Duration of use/ Pattern of use	Information obtained on past and current OC use through direct patient questionnaire; duration of current use incorporated into regression model
Attrition of susceptibles/ Healthy user effect	Statistical analysis (regression model) incorporated important baseline risk factors
Prescription bias	Statistical analysis (regression model) incorporated important baseline risk factors (personal history of VTE, family history of VTE, BMI, duration of COC use, chronic disease, concomitant medication, education level and smoking)
Validity of diagnosis For VTE	Medical records review / Adjudication by 3 exposure-blinded experts

Strengths:

- Cases validated through medical chart review; adjudication through 3 treatment-blinded physicians
- Accounting for confounding factors such as history (personal and family) of VTE, duration of current COC use, BMI, smoking
- Controls are selected from the matching community, in random manner

Limitations:

- OC use ascertained based on patient report; potential differential recall of COC use in cases vs. controls
- Excluded fatal VTE cases (potential for Neyman's bias)
- Reporting physician was not blinded to type of OC
- Inclusion in study required patient consent

In the sponsor's opinion, this case control study used a study methodology that was not as robust as the Ingenix and EURAS studies, but is clearly superior to the MEGA study. However, this case-control study does incorporate key design elements that allows for adequately accounting for key confounders in ascertaining the risk of VTE when comparing different COCs. For example, controls are selected in a truly random manner while being matched for key risk factors and confounders; cases were validated through direct blinded review of medical records. The results of this study are compatible with the results reported in the published prospective Ingenix and EURAS studies. This study also helps to illustrate the likelihood for case-control and cohort studies to reach the same correct conclusion when good research methods are used.

4.7.1.8 PharMetrics study (Jick and Hernandez, 2011)

The sponsor's assessment of the Jick publication was initially submitted to the FDA in April 2011 in response to this publication. Details are provided in [Section 10.2](#), [\(Appendix 2\)](#).

Table 4-16: Structured Summary of Study Design as Reported by the Authors – PharMetrics Study

PharMetrics Study, Jick and Hernandez 2011	
METHOD	
Objective	To compare the risk of idiopathic non-fatal VTE in current users of Yasmin relative to current users of preparations containing LNG.
Study Design	Observational cohort study with nested case-control analysis
Geography	USA
Time Period	January 2002 to December 2008
Population / Source of Data	PharMetrics database (a US-based company that collects information on claims paid by managed care plans; it contains information on paid claims for drugs, medical diagnoses, and procedures, as well as patient's birth year and sex). Cohort included all women ages 15-44 years without major risk factors for VTE who received an OC containing either DRSP (Yasmin) or LNG after January 1, 2002. Cases: First time recorded claim for non-fatal idiopathic VTE Controls: Matched by birth year and index date; 4 controls matched to each case
Sample size	Cohort: 937,408 women who satisfied all the conditions for inclusion in this study / Yasmin: 392,844 WY LNG-COCs: 521,824 WY Cases: 186 / Yasmin: 121 LNG-COCs: 65 Controls: 681 / Yasmin: 313 LNG-COCs: 368

ASSIGNMENT	
Baseline exclusion criteria	Risk factors for VTE, such as any history of cancer (other than nonmelanoma skin cancer), renal failure, chronic cardiovascular disease, or inflammatory or autoimmune conditions
Assessment of COC use	COC use based on a recorded claim for a prescription of a study contraceptive whose filled use extended to within 30 days before the index date or beyond the index date
Comparator	LNG-containing COCs, 0.02 mg and 0.03 mg EE
Method to address confounding	Age, calendar time (date of diagnosis), and duration of use If influenced risk <10%, not considered a material confounder

ASSESSMENT	
VTE Definition	First time recorded claim for a clinically diagnosed VTE (DVT or PE) with a hospital admission, a visit to the emergency room, or a positive indication of VTE from diagnostic test results, and who subsequently received prolonged anticoagulation treatment and no subsequent OC use. Did not include fatal cases.
VTE Validation Process	None specified.

RESULTS

The incidence rates for VTE³:

DRSP: 3.08/10,000 WY (95% CI 2.56 to 3.68)

LNG-COCs: 1.25 / 10,000 WY (95% CI (0.961 to 1.59)

Odds ratio for VTE for Yasmin vs. LNG-COCs, overall analysis:

2.3 (95% CI 1.6 to 3.2, unadjusted)

2.4 (95% CI 1.7 to 3.4, adjusted for duration of exposure) (Ref Table 2 of the publication).

Multiple stratified subanalyses were also performed

INTERPRETATION

The risk of non-fatal VTE among DRSP-COC users (Yasmin) seems to be around twice that of users of OCs containing LNG.

Key Factor	Approach
Duration of use/ Pattern of use	Subanalyses stratified based on duration of use and new user versus unknown duration of use. Duration of use defined as the time interval (in months) from the first use of a COC within the current episode of use until the index date; duration of use defined as “unknown” if current episode of use began within 4 months of the start of the computer record. New episode of use defined as previous use with a gap of at least 100 days before the current episode of use or if no previous prescription for an OC in record and at least 4 months of recorded history.
Attrition of susceptibles/ Healthy user effect	Subanalyses to attempt adjustment for factors such as menstrual disorder diagnosis, age, however much of the important information not captured in the database. Women with risk factors for VTE removed prior to case assignment, however, may have created additional confounding based on length of time in database and increasing age.
Prescription bias	Subanalyses to attempt adjustment for factors such as menstrual disorder diagnosis, age, however much of the important information not captured in the database.
Validity of diagnosis For VTE	No validation performed

Strengths:

- Exposed subjects identified without prior knowledge of outcome (VTE) (prospectively assembled cohort)
- Selection of cases and controls blinded to type of OC used
- Matching of cases and controls based on age and index year
- Analysis of new users versus users of unknown duration performed

³ The publication reports incidence rates per 100,000 WY. Within this document, all incidence rates are reported as per 10,000 WY, to enable comparison across studies.

Limitations:

- No validation of cases through medical records
- Limited information on baseline risk factors due to short pre-index period of 6 months
- Poor measure of BMI; Obesity entry in database used for adjustment, however, proportion of patient with ICD-9 code entry for obesity likely unreliable
- No information on family history
- The risk of being excluded increases with increasing age due to the fact that time to diagnosis for most chronic diseases is rather long. In this study the LNG group is older than the DRSP group and is therefore subject to more exclusions which lead to a selection bias in the selection of cases.
- Failure to show distribution of exclusions between exposure groups
- Evaluation of ‘idiopathic cases’ only: no standard for classification into idiopathic and non-idiopathic cases; underlying family history, and therefore underlying cause, could not be analyzed
- No analysis takes into account all confounding factors (only multiple subanalyses are reported);
- Large number of users of unknown duration of use; incomplete accounting for duration of use; “After adjustment for duration of exposure the odds ratio was virtually unchanged.”
- Does not account for fatal VTE (potential for Neyman’s bias)

The sponsor has many concerns with this study. The overall generalizability of the findings, limited to non-fatal idiopathic VTEs, is questionable. This concern is accentuated by the fact that this group of investigators has been inconsistent in how they define non-fatal idiopathic VTEs ([Table 4-17](#)).

Table 4-17: Criteria Used to Exclude Subjects From Inclusion into “Idiopathic Cases” Category Reported by Jick et al in Studies of LNG-COC

Exclusion criteria	2006 (Jick et al., 2006)	2010 (Jick et al., 2010)	PharMetrics 2011 (Jick and Hernandez, 2011)	GPRD 2011 (Parkin et al., 2011)
Important lower-limb injury	yes		yes	
Major injury				yes
Prolonged immobility				yes
Invasive / major surgery	yes		yes	yes
Recent (within 90 days) major surgery		yes		
(Severe) trauma	yes	yes	yes	
Epilepsy		yes		
Pregnancy	yes	yes	yes	yes

The lead author has commented previously in the scientific literature on the essential need to perform VTE case validation from the clinical records in this type of database study. Paradoxically, this essential step was not done in this study. The results must therefore be viewed as invalid, based on the lead author's own prior statements, common research standards, and the draft recommendations of the FDA for database studies.

The lack of validation of cases, the authors' erratic definitions of non-fatal idiopathic VTE, and other aspects of how they process data from the PharMetrics database raise concerns that their results are highly unreliable. Support for this concern becomes clear when one compares the reported rates of VTE across studies by these investigators, from the PharMetrics database, over roughly a comparable era. Between studies, the authors present event rates that are over 3-fold different for what should be a comparable population of women using comparable LNG-COCs ([Table 4-18](#)).

Table 4-18: Studies on VTE and Contraceptives – Idiopathic VTE Event Rates for LNG Subjects Only From the PharMetrics Database

Study	VTEs Number of Cases	Database	Timeframe	Event Rate (10,000 WY)	Event rate (10,000 WY) (95% CI)
Jick et al., Contraception 73 (2006) 566- 70	70	PharMetrics	January 2000 – March 2005	LNG-0.03 mg 2.71	2.11-3.43
Jick et al., Contraception 81 (2010), 16-21	16	PharMetrics	April 1 2002 – March 2006	LNG-0.03 mg 3.80	2.34 – 6.17
Jick et al., BMJ 2011; 340:d2151	65	PharMetrics	Jan 1 2002 – Dec 31 2008	LNG-(0.02 or 0.03 mg) 1.25	0.96 – 1.59

While the sponsor has highlighted other concerns in its full assessment to the FDA, its overall conclusion is that the reliability of the findings and the conclusions reached by the authors are invalid.

4.7.1.9 GPRD study (Parkin et al., 2011)

The sponsor's assessment of the Parkin publication was initially submitted to the FDA in April 2011 in response to this publication. Details are provided in [Section 10.2 \(Appendix 2\)](#).

Table 4-19: Structured Summary of Study Design as Reported by the Authors – GPRD Study

GPRD study Parkin et al 2011 (BMJ)	
METHOD	
Objectives	To examine the risk of non-fatal idiopathic VTE in current users of Yasmin relative to current users of preparations containing LNG.
Study Design	Observational cohort study with nested-case control analysis
Geography	UK
Time Period	May 2002 to September 2009
Population / Source of Data	UK General Practice Research Database (information derived from general practice records, including demographic data, prescribed drugs, medical diagnosis, hospital admissions and death) Cohort: Women age 15-44 years without major risk factors for VTE who started a new episode of use of COC containing 0.03mg of estrogen in combination with either DRSP (Yasmin) or LNG. Cases: Women with a first diagnosis of VTE Controls: Matched by age, duration of recorded information, general practice; up to 4 controls matched to each case
Sample size	Cohort: 318,825 women who satisfied all the criteria for inclusion in the study cohort/ Yasmin: 73,853 WY; LNG-COCs: 482,229 WY Cases: 61/ Yasmin: 17 LNG-COCs 44 Controls: 215/ Yasmin: 26 LNG-COCs 189

ASSIGNMENT	
Baseline exclusion criteria	<p>Prior to selection of cases/controls, potential subjects were removed from base population if information in database indicated presence of risk factors for VTE as well as conditions that might influence decisions of prescribing of COCs: previous VTE, cancer (except non-melanoma skin cancer), chronic renal failure, MI, stroke, other cardiovascular disease, treated hypertension, treated hyperlipidemia, type I diabetes, ulcerative and other colitis, systemic lupus erythematosus (SLE), rheumatoid arthritis, ankylosing spondylitis and other spondylopathies, psoriatic arthritis, cystic fibrosis, injecting drug use, and coagulation defects.</p> <p>After selection of cases/controls, blinded reviewers excluded women who had a record of pregnancy, surgery, major injury, or prolonged immobility in the three months before the index date.</p> <p>Continuous use of OC prior to May 1, 2002</p>
Assessment of COC use	<p>Current users defined as women who received a prescription that would have extended to the index date or to within 30 days of that date. The WY of use for DRSP and LNG COCs in the study cohort was counted as the time from the date of the first prescription in each episode of use until the end of the last prescription plus 45 days.</p>
Comparator	LNG-containing COCs, 30ug EE
Method to address confounding	BMI, history of varicose veins, smoking status (non-smoker, current smoker, past smoker), antidepressant use, and duration of the current episode of OC use

ASSESSMENT	
VTE Definition	<p>Diagnoses of VTE (DVT or PE) were based on Read and OXMIS codes.</p> <p>Women who did not have a record of treatment with an anticoagulant, as well as any women who continued to receive prescriptions for OCs after the index date were excluded as cases, because the validity of the diagnosis of VTE was less certain in such women.</p>
VTE Validation Process	<p>Out of 65 cases, hospital discharge or outpatient clinic letters were requested of 42 (65%) cases in sequential order; out of these, 31 (48% of total cases) were received and reviewed. Out of these 31 cases, 4 cases were excluded and 2 cases, where “information received was minimal and we could not determine whether the diagnosis...had been made on the basis of objective tests” were retained as valid cases. No validation on remaining 34 cases</p>

RESULTS
<p>Total: 61 idiopathic VTEs / Yasmin 17 LNG-COCs 44</p> <p>Incidence rate of VTE (Crude)⁴</p> <p>Yasmin: 2.3/10,000 WY (95% CI 1.34-3.69)</p> <p>LNG-COCs: 0.91/10,000 WY (95% CI 0.66-1.22)</p> <p>Matched analysis involving all cases and controls (overall analysis) (Ref Table 2): Odds Ratio of Yasmin vs. LNG</p> <p>Crude: 3.2 (95% CI 1.5-7.0)</p> <p>Adjusted: 3.3 (95% CI 1.4-7.6) (adjusted for BMI as continuous variable; missing values for BMI and smoking imputed)</p> <p>Multiple additional matched subanalyses.</p>
INTERPRETATION
COCs containing DRSP carry a higher risk of VTE than do formulations containing LNG.

KEY FACTOR	APPROACH
Duration of use/ Pattern of use	Duration of current episode of use / no analysis of pattern of use
Attrition of susceptibles/ Healthy user effect	“idiopathic cases” only / Baseline exclusion by risk factors for VTE as well as conditions that might influence decisions of prescribing of COCs
Prescription bias	“idiopathic cases” only / Baseline exclusion by risk factors for VTE as well as conditions that might influence decisions of prescribing of COCs.
Validity of diagnosis For VTE	Hospital discharge or outpatient clinic letters of 31 cases (out of 65) were reviewed; Use of surrogate measures (use of anticoagulant, no subsequent OC use) to verify additional cases

Strengths:

- Exposed subjects identified without prior knowledge of outcome (VTE) (prospectively assembled cohort)
- Inclusion of several confounding factors: BMI, smoking, history of varicose veins, antidepressant use, and current duration of COC use
- Matching of cases and controls based on age, BMI (partially imputed) and smoking
- Selection of cases and controls blinded to type of OC

Limitations:

- GPRD represents the UK general practice physicians; Yasmin is frequently under formulary restriction in the UK, and therefore, its use in clinical practice in the UK

⁴ The publication reports incidence rates per 100,000 WY. Within this document, all incidence rates are reported as per 10,000 WY, to enable comparison across studies.

is likely to differ markedly, in terms of characteristics of candidate patients and users, from the broadly used LNG-COCs. (prescribing bias)

- Less than 50% of cases were validated with medical records; Use of surrogate measures (use of anticoagulation, no subsequent OC use) ‘verified’ cases
- Missing data on confounding factors were imputed
- 61 cases of VTE were distributed to 27 DVT and 34 PE, and entirely unexplained. Implies gross under-ascertainment of DVTs
- Duration of recorded medical information used to exclude subjects not standardized (minimum 1 year, mean duration 10 years), potentially creating differential baseline risk of VTE (older subjects more likely to be excluded from study)
- Failure to show distribution of exclusions between exposures
- Low number of Yasmin cases
- Evaluation of ‘idiopathic cases’ only: no standard for classification into idiopathic and non-idiopathic cases; underlying family history, and therefore underlying cause, could not be analyzed
- Does not account for fatal VTE (potential for Neyman’s bias)

The sponsor’s major concern about this study revolve around the significant differences in the pattern of use of Yasmin and LNG-COCs in the UK. LNG-containing COCs are among the most widely used preparations and available to the vast majority of women, without administrative restrictions, at minimal cost. By contrast, Yasmin is restricted in many formularies, not even available in many regions, and generally reserved for women who cannot tolerate other COCs or have specific medical needs. There is no evidence that the authors addressed these significant differences. The lack of reliability of the reported results is demonstrated by the implausible ratio of DVT to PE cases.

4.7.1.10 FDA-funded study

On 27 October 2011 the FDA posted the results of the FDA-funded study on “Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints” to their drug safety communication website. The objective of this study was to assess VTE, ATE (including AMI and stroke), all-cause cardiovascular mortality and total mortality for several newly approved CHCs (early 2000s) – specifically Yasmin, Ortho-Evra, and Nuvaring - compared to users of older COC (Comparators) preparations containing the progestins LNG, norethindrone, or NGM combined with 0.02 mg to 0.035 mg EE.

4.7.1.10.1 Data on VTE

Table 4-20: Structured Summary of Study Design as Reported by the Investigators for VTE – FDA-Funded Study

FDA-funded study, released 27 October 2011	
METHOD	
Objectives	To determine prevalence and incidence rates for ATE and VTE events and all-cause and cause-specific mortality in women exposed to 3 newer hormonal contraceptives compared to older frequently prescribed low estrogen hormonal contraceptives
Study Design	Retrospective Cohort Study
Geography	USA
Time Period	January 2001 to December 2007
Population / Source of Data	<p>Computerized data files from:</p> <ul style="list-style-type: none"> • Kaiser Permanente, northern California • Kaiser Permanente, southern California • Washington state Medicaid program • Tennessee state Medicaid program <p>Computerized files included demographic data, ambulatory prescriptions from pharmacy records or claims, hospitalization and outpatient visit data with diagnoses from health plan records or claims; mortality obtained from state mortality files. For inpatient ATE and VTE cases, follow up in written medical records</p> <p>Cohort included all women ages 10-55 years, who had at least one prescription for a study COC between 1 January 2001 and 31 December 2007, and who had at least 6 months of continuous membership in a plan prior to the Rx (Women in Washington state cohort were required to have at least 5 months of eligibility – no explanation provided for reduced period).</p>
Sample size	<p>Yasmin: 142,166 (189,210 WY)</p> <p>LNG2 (0.03 mg EE): 198,839 (244,607 WY)</p> <p>COMP group (all doses LNG, norethindrone acetate [NETA], NGM combined): 586,278 (617,265 WY)</p> <p>Also included NGM transdermal patch (NGMN) and etonogestrel vaginal ring (ETON)</p> <p>Overall: 835,826 (898,251 WY)</p>

ASSIGNMENT	
Baseline exclusion criteria	Subject excluded if suffering from serious or life threatening illness during pre-exposure eligibility period (sickle cell disease, cystic fibrosis, cerebral palsy, cancer, HIV, organ transplant, liver failure, severe congestive heart failure [CHF], renal failure, respiratory failure, or hospitalization for AMI, stroke, or VTE), pregnancy
Assessment of COC use	COC use based on data from pharmacy records; Subject considered new user on the basis of no prior COC use in the previous 6 months. Duration of use ascertained through evidence of prescriptions in database.
Comparator	Two comparator groups used: COMP group consisted of all doses of LNG, NETA, and NGM COCs combined; “LNG2” (0.03 mg EE/LNG)
Method to address confounding	Cox proportional hazards models included age, site and calendar year of entry into study (Models that included ATE or CVD mortality also included hypertension, hyperlipidemia, and diabetes as fixed covariates). Separate analyses were provided for new users. Analyses in new users were stratified by duration of use.

ASSESSMENT	
VTE Definition	Hospitalization diagnosis codes for VTE or ATE; DVT diagnosed as an outpatient required code for DVT plus first prescription for an anticoagulant during the 30-day period subsequent to the diagnosis
VTE Validation Process	Hospitalized: medical record abstracted and sent to centrally adjudication physician for review and blinded adjudication. 10% sample of cases independently reviewed by a second blinded adjudicator Outpatient: medical records for 103 potential events at one site reviewed by Principal Investigator; 92 (89.3%) validated as events. An additional 128 outpatient events from other sites not reviewed or validated

VTE RESULTS	
<p>VTE Event Rates (n): all users, unadjusted (Sponsor-derived calculation from Table 10b)</p> <p>Yasmin: 7.61/10,000WY (144)</p> <p>LNG2: 6.58/10,000 WY (161)</p> <p>COMP: 6.30/10,000 WY (389)</p>	
<p>VTE Event Rates (n): age and site adjusted, all users</p> <p>Yasmin: 10.22/10,000 WY (144)</p> <p>LNG2: 6.64/10,000 WY (161)</p> <p>COMP: 5.96/10,000 WY (389)</p>	
<p>Crude incidence rate ratio Yasmin versus LNG2: 1.16</p> <p>Yasmin versus COMP: 1.21 (Sponsor-derived calculation from Table 10b)</p>	
<p>Hazard ratio adjusted for age, site, year of entry into study</p> <p>Yasmin versus LNG2: 1.45 (95%CI 1.15-1.83)*</p> <p>Yasmin versus COMP: 1.74 (95%CI 1.42-2.14)</p>	
INTERPRETATION - Author's overall conclusion for VTE	
<p>In adjusted analyses, DRSP was associated with a significantly higher risk of VTE relative to low-estrogen comparators (eg, LNG)</p>	

KEY SOURCE OF BIAS	APPROACH
Duration of use/ Pattern of use	Prescription data-based analysis for <3 months, 3-6 months, 6-12 months, > 12 months / EMR exposure periods may not represent actual exposure pattern; pregnancy dates may be inaccurate
Attrition of susceptibles/ Healthy user effect	Unable to distinguish between first-time ever users and new users / No information on BMI, obesity, family history of VTE, smoking
Prescription bias	Acknowledged difference in patients treated with different formulations, (interaction by site); no explanation provided ("it is unclear why this is the case" p.29)
Validity of VTE diagnosis	Review of medical records for all inpatient events; outpatient cases validated only at one site

Strengths:

- Large population size and number of events; community based 'real-world' data
- Validation of inpatient events by blinded adjudication and patient medical records
- New user analyses stratified by duration of use: (<3 months, 4-6 months, 7-12 months, and >12 months)
- Inclusion of fatal cases

Limitations:

- Data collection started January 2001, prior to the launch of the three products under investigation
- No differentiation made between first-time ever users and new users. Age distribution of the groups, especially at the Kaiser sites, makes it likely there were more first time ever users in the Yasmin cohort (Attrition of susceptibles).
- For new users, the only nominally significantly increased risk for VTE associated with Yasmin use was in the younger 10-34 years age group relative to both the combined comparator and LNG2 group (attrition of susceptibles)
- Validation of outpatient DVTs only performed at one site
- Inadequate control for prescriber bias (no information on BMI/obesity, family history of VTE; limited information on personal history VTE, smoking). Only 6 months of prior information available
- Prescribing pattern might drive effects (The formulary restrictions in the databases are not described by the authors. For the Kaiser sites, there seems to be a specific pattern of CHC use in the different age groups which might be driven by underlying prescribing recommendations given to affiliated physicians.)
- As noted, there is an imbalance between COC groups for the covariate age, particularly at the Kaiser sites (prescriber bias)
- Bias introduced by testing “potential covariates” individually according to effect of each on the risk estimate, excluding the covariate if change in risk estimate did not exceed 10%.

4.7.1.10.2 Data on ATE

Table 4-21: Structured Summary of Study Design as Reported by the Investigators for ATE – FDA Funded Study

FDA-funded study, released 27 October 2011	
METHOD - As Described in VTE Section above	
ASSIGNMENT	
Baseline exclusion criteria	As described in VTE section above
Assessment of COC use	As described in VTE section above
Comparator	As described in VTE section above
Method to address confounding	Cox proportional hazards models included age, site and calendar year of entry into study (Models that included ATE or CVD mortality also included hypertension, hyperlipidemia, and diabetes as fixed covariates). Separate analyses were provided for new users. Analyses in new users were stratified by duration of use.

ASSESSMENT	
ATE Definition	Hospitalization diagnosis codes for ATE (AMI, Ischemic stroke)
ATE Validation Process	<p>Medical record abstracted and sent to physician for review and blinded adjudication by 2 physicians; one specialist (cardiologist for all AMIs, neurologist for most strokes) and 1 internist. 10% sample of cases independently reviewed by a second blinded adjudicator</p> <p>AMI: combination of clinical symptoms, blood biomarkers, ECG findings, resulting in 'definite', 'probable', and 'suspect' cases</p> <p>Stroke: 1) final physician diagnosis has occurred, and 2) satisfies appropriate algorithm</p>

Results for ATE:

In total, 138 ATEs (78 strokes and 60 MIs) were observed in the study:

ATE Event Rates (n): unadjusted, all users (calculated by the sponsor from Table 10a)

Yasmin: 0.90/10,000 WY (17)

LNG2: 1.80/10,000 WY (44)

COMP: 1.75/10,000 WY (108)

ATE Event Rates (n): age and site adjusted, all users

Yasmin: 1.08 /10,000 WY (17)

LNG2: 1.64 /10,000 WY (44)

COMP: 1.44 /10,000 WY (108)

Incidence Rate ratio (unadjusted), for all users (calculated by the sponsor from Table 10a)

Yasmin versus LNG2: 0.50

Yasmin versus COMP: 0.51

Hazard ratio (adjusted for age, site, year of study entry, hypertension, hyperlipidemia, and diabetes) - All sites, all users:

Yasmin versus LNG2: 0.99 (95%CI 0.58-1.69)

Yasmin versus COMP: 0.81 (95%CI 0.45-1.44)

Interpretation / Authors' Conclusion for ATE:

Yasmin was associated with higher risk for ATE in new users overall with this finding restricted to women in the 35-55 years age group only.

Strengths: (retained items from prior sections pertaining to VTE are italicized)

- *Large population size and number of events; community based 'real-world' data*
- *Validation of inpatient events by blinded adjudication and patient medical records*
- *New user analyses stratified by duration of use (<3 months, 4-6 months, 7-12 months and >12 months)*
- *Inclusion of fatal cases*

Limitations: (in addition to items from prior sections pertaining to VTE)

- Overall, highest incidence rates (both crude rate and rate adjusted for age and site) are for LNG2 and COMP, not for Yasmin. Only after multiple subanalyses, is it reported that there is a nominally significantly increased risk for ATE associated with Yasmin in the older 35-55 years age group, and only for new users.

Overall Conclusions (VTE/ATE)

Based on an initial assessment of this recent report, there appear to be numerous design, methodological, and statistical flaws such that the results of the FDA-sponsored study are not reliable. This conclusion is based on four major areas summarized below:

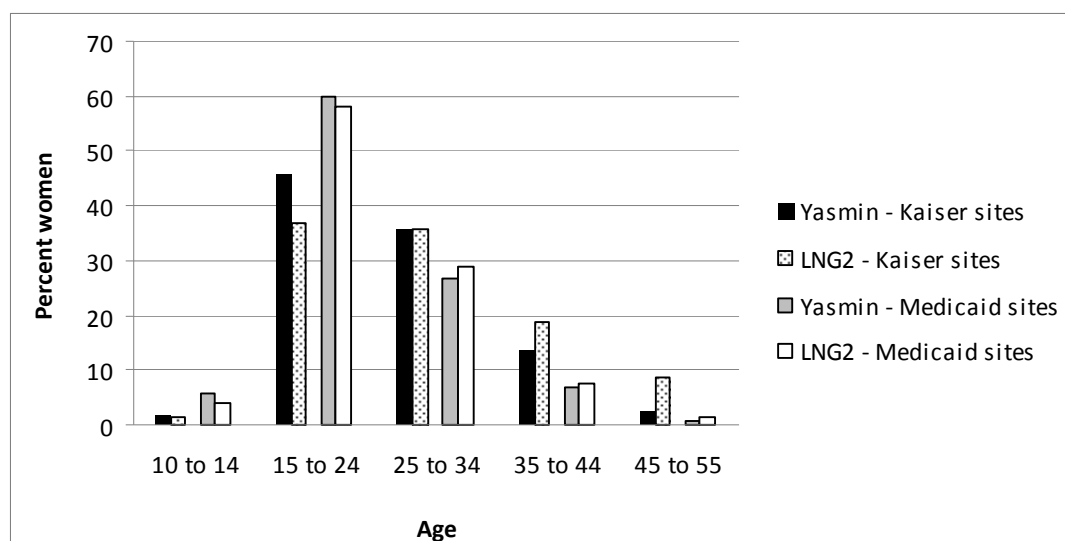
1. Inability to account for important key confounders due to either missing (eg, personal history of VTE), or totally unavailable (BMI, family history of VTE) data.
2. Lack of internal consistency of results:
 - Yasmin with reported higher VTE and ATE rates, yet statistically significant lower death rates.

Table 4-22: Relative Hazard Ratios - Yasmin versus Comparators for Study Endpoints

	VTE HR	ATE HR	CVD Mortality	Total Mortality
Yasmin vs. LNG-2				
All Users	1.74 (1.42 - 2.14)	0.99 (0.58 - 1.69)	0.37 (0.11 - 1.25)	0.85 (0.59 - 1.23)
New Users	1.57 (1.13-2.18)	1.64 (0.79 - 3.40)	0.57 (0.05 – 6.35)	0.57 (0.32 – 1.02)
Yasmin vs. COMP				
All Users	1.45 (1.15 - 1.83)	0.81 (0.45 - 1.44)	0.33 (0.09 - 1.18)	0.66 (0.45 - 0.99)
New Users	1.77 (1.33 - 2.35)	2.01 (1.06 - 3.81)	0.25 (0.03 – 1.95)	0.88 (0.52 – 1.53)

- Pattern of risk (IRR) over time for Yasmin inconsistent and not biologically plausible. Results demonstrate an elevated risk at 0-3 months, no elevated risk at 4 to 6 months, an elevated risk at 7-12 months, and no elevated risk >12 months.
- While the study purports to demonstrate a significant increased risk of ATE with Yasmin, the highest age-adjusted, site-adjusted rate overall was found for the LNG2 cohort. The only nominally statistically significantly increased risk for ATE was in the older 35-55 years age group, and only for new users. When this new user group is further split up by duration of use, no statistically significant increased risk was reported. When stratified by site, a significant effect in new users was reported only in the Kaiser sites [HR 2.9 (95% CI 1.41-6.0)], while the Medicaid sites provided an estimate of effect in the opposite direction not significant from the null hypothesis of no association [HR 0.39 (95% CI 0.05-3.05)]. This substantial heterogeneity of results among sites suggests that factors other than Yasmin explain these associations.
- Yasmin cohorts at Kaiser have a substantially different age distribution than LNG2 or COMP groups, with a higher proportion of younger users in the Yasmin group. This group is more likely to contain a higher proportion of first-ever users.

Figure 4-6: Age distribution of Yasmin and LNG2 users at Kaiser and Medicaid sites



3. Design issues:

- Definition of VTE:
 - Inpatient – 60/92 (65%) MIs validated; 78/241 (32%) of strokes validated, 405/614 (66%) of VTEs validated
 - Validation of outpatient DVTs only performed at northern California Kaiser site by the PI [92 out of 103 (89.3%)] confirmed as VTEs, which is very high. This proportion of validated cases does not necessarily apply to sites located in Tennessee, Washington, and southern California where different standards of care may exist. At Tennessee, Washington, southern California Kaiser sites, no validation attempted, leaving 128 outpatient VTEs not validated (20% of the total VTE cases). This may differentially affect the results if younger patients are more likely to be evaluated for a VTE in the outpatient setting.
- Inclusion years (2001 to 2007) do not make sense. Data collection started January 2001, prior to the launch of the three products under investigation: Yasmin launched in July 2001, Nuvaring in July 2002, and Ortho Evra in May 2002. No reason stated for why data not collected beyond 2007. While study purports to investigate the difference in VTE rates based on type of progestin, the type of progestin and how recently it was introduced to the market are confounded. The study does not include any COC with a “newer” progestin marketed prior to 2001 (eg, DSG-containing COCs have been available since 1992 but are not included in the study), which could help make this distinction. First time ever users of COCs (the group at highest risk for VTE) are more likely to be prescribed newly launched products. (Lewis et al., 1996)

4. Statistical Issues

- Unlike all other studies included in this review, the authors do not present crude incidence rates for VTE. These sponsor-derived rates were calculated from Table 10b for all users and for new users for Yasmin, COMP, and LNG2:
 - All users (crude IR/10,000 WY): Yasmin (7.61/10,000 WY); COMP (6.3/10,000 WY); LNG2 (6.58/10,000 WY)
 - New users (crude IR/10,000 WY): Yasmin (9.23/10,000 WY); COMP (8.27/10,000 WY); LNG2 (7.61/10,000 WY)

Age and site adjustment cause crude IR for Yasmin to go from 7.61 to 10.22, while, for example, LNG2, the adjustment led to only minor changes (crude 6.58 to 6.64 adjusted), suggesting a major imbalance between groups based on age that had a substantial differential effect on the adjusted rates.

- Tables provided in the report and appendices indicate highly statistically significant imbalances (table 7) for many of the covariates recorded. Application of regression methods (Cox proportional hazard) in cases of major imbalances is unreliable. Alternative methods are available to simulate balance of known covariates as in a randomized clinical trial (eg, propensity score matching).
- No clear distinction between primary analysis and exploratory secondary analyses; multiple analyses performed with no adjustment for multiple comparisons
- Covariates not selected *a priori*. Authors evaluated approximately 40 potential covariates (in addition to those included in the regression models) by entering each in the basic regression models, with a decision to include it in further model testing if the estimate of relative risk associated with any of the study COCs (versus comparators) was changed by 10% or more; all were excluded based on this process. Selection of covariates based on their effect on the outcome data is inappropriate and known to introduce bias.
- Despite the large size of the three cohorts, the investigators themselves noted that the findings with LNG2 as the comparator generally paralleled the findings for the combined comparators, though not as many reached statistical significance. The most comparable group for comparison to Yasmin in this study appears to be the LNG2 group as the COMP group contains COCs containing 0.02 mg of EE. Also, when looking at the NETA component of the COMP group, the mean age of NETA users is 33.4 years, clearly representing a very different cohort from the Yasmin users. The rationale for creating the COMP group is unclear.

The results posted on the FDA website have been represented as a final study report. At the same time, the FDA stated in its initial posting about the current study that: *“It was recognized at the time (sic of initiation of the study) that a more in-depth assessment of potential reasons for increased risk would not be possible using only claims and electronic medical records and would require physician and patient contact, something that could be conducted later if needed.”* This statement raises the possibility that the current study report may constitute an interim work product to be followed by future,

more comprehensive data collections and more rigorous analyses. It also acknowledges some of the serious limitations of the current study.

Based on the currently-released data, this study suffers from significant methodological flaws. The overall ATE results clearly demonstrate no increased risk of ATE. The VTE results are inconsistent – even within subgroups of the study. This inconsistency, as well as lack of control for key confounding factors, renders the results of the study unreliable.

4.7.1.11 Additional considerations

4.7.1.11.1 Selection of an appropriate comparator

A fundamental question in comparing the risk of VTE between different COCs is the choice of an appropriate comparator. Arguably the most important question in advising women contemplating the use of COCs is their risk compared to non-use as well as the risk compared to pregnancy. Despite the critical nature of this question, there are limited data available.

In the absence of data for non-users, studies have selected various comparators. LNG-containing COCs have been the reference preparation for many studies, including those reviewed here. One of the major challenges in using LNG-containing COCs as a reference preparation is that the use patterns for LNG-containing COCs vary greatly between countries; LNG-containing COCs are the predominant formulation in the UK and Canada, but their use relative to other COCs has decreased markedly over the years in the US and a number of European countries.

If one compares across recent studies the rates of VTE reported for LNG-COC users, one can appreciate wide variations, ranging from 3.21 to 8.0 per 10,000 WY ([Table 4-23](#)), a 2.5 fold difference in range. The variability in reported rates from database studies focusing on idiopathic VTE only is even greater, ranging from 0.9 to 3.80, a 4.2 fold difference. Given the wide variation in the reported event rates for LNG-COC users, and the highly likely influence of prescription bias, the sponsor proposes that the selection of LNG as a standalone comparator is ill-advised, especially in the US context. This is of greatest relevance when evaluating the studies by Jick et al (2011) and Parkin et al (2011), where LNG-COCs were the only comparator. It also applies to the van Hylckama Vlieg et al (2009), and the Lidegaard et al (2009) studies (and the reanalysis), where the results are primarily presented relative to the risk for LNG-COC users.

Table 4-23: VTE Rates for LNG-COC Users Across a Number of Studies

LNG	VTE Incidence rate (events per 10,000 WY)	CI	Reference
EURAS 2007	8.0	5.2-11.7	(Dinger et al., 2007)
Danish Cohort 2009	5.8	NA	(Lidegaard et al., 2009)
PharMetrics 2011 (Extrapolated from 39% of cases as idiopathic)	3.21	NA	(Jick and Hernandez, 2011)
Studies in UK GPRD Database – Idiopathic VTE cases only			
Jick et al. 1995	1.6	NA	(Jick et al., 1995)
Farmer 1999	3.4	NA	(Farmer et al., 1999)
Jick 2000	2.3	NA	(Jick et al., 2000)
Parkin et al. 2011 (with Jick)	0.9	0.66- 1.22	(Parkin et al., 2011)
Studies in US Databases – Jick et al – Idiopathic VTE Cases Only			
PharMetrics 2006	2.71	2.11 – 3.43	(Jick et al., 2006)
PharMetrics 2010	3.80	2.34 – 6.17	(Jick et al., 2010)
PharMetrics 2011	1.25	0.96 – 1.59	(Jick and Hernandez, 2011)
Marketscan 2010	1.99	1.51 – 2.63	(Jick et al., 2010)

A more reasonable approach is to compare one formulation to all other COCs in use within the population studied. This is really the question that confronts US clinicians and women as they select among a variety of COCs.

Some have argued that studies should compare between COCs on the basis of the progestin contained in each COC. This is an extension of the approach described above for LNG-COCs, and suffers from the same underlying challenges. It does offer the potential for an internal control within a study, but given the very inconsistent findings across studies in this field, this is overall unlikely. The approach of breaking down comparators on the basis of each progestin is only relevant if there is already compelling evidence that there is a difference in the risk of VTE for a given progestin compared to others. The sponsor does not feel that such incontrovertible evidence exists at present. Even when comparing only among so-called 2nd generation progestins, the relative risk of VTE varies widely. In the Lidegaard et al study (Lidegaard et al., 2009) using LNG-COC

as the reference, estimates ranged from 0.98 for norethisterone to 1.19 for NGM. The companion publication from 2009 ([van Hylckama Vlieg et al., 2009](#)) reported ratios compared to LNG-COCs of 1.1 for norethisterone and 1.6 for NGM. It is, therefore, appropriate to consider that the most clinically relevant comparator is the aggregate universe of low-dose COCs currently available in clinical practice. This was the approach used in Ingenix, EURAS, and LASS and it showed that the risk of VTE with Yasmin was similar to the COCs studied.

4.7.2 Overall conclusions about the risk of VTE with Yasmin

As stated earlier, no observational study design is perfect and each has its own set of limitations. Nonetheless, it is important to design a study taking into account known biases that are relevant to the specific dynamics of the scientific question at hand. In looking at the current set of studies, the Ingenix, EURAS, LASS, and German Case-Control studies avoid bias well. All 4 studies find that the risk of VTE for Yasmin is similar to the reference COCs studied, including LNG-COCs. By contrast, the Danish (and Lidegaard reanalysis), MEGA, US PharMetrics, UK GPRD studies, as well as the FDA-funded study each present serious methodologic limitations that undermine the validity of their findings. The sponsor's overall conclusion is that based on the best currently available evidence and contemporary scientific standards, the risk of VTE for Yasmin is similar to that seen for LNG-containing COCs, as well as the other COCs studied.

The sponsor is committed to patient safety. From the onset, the sponsor was committed to monitoring the safety and validating a positive benefit-risk profile for Yasmin when used as directed. This commitment has been reflected in the conduct of the Ingenix study and the EURAS/LASS studies. All of these studies were undertaken in consultation with major Regulatory Authorities (FDA, EMA) and conducted in a timely manner. Final study reports, publications, and interim study reports, as the studies progressed, were shared on an ongoing basis with the FDA and other regulatory authorities around the world.

The sponsor reaffirms that, based on the best available scientific evidence, the risk of developing VTE or blood clots in women using Yasmin is comparable to other combination birth control pills studied, including those containing LNG.

4.8 Studies on the risk of VTE with YAZ

4.8.1 Prospective studies

In contrast to Yasmin, to the sponsor's knowledge, the only dataset focusing specifically on the risk of VTE with YAZ is based on the INAS-OC study. The 2011 BMJ publication by Lidegaard et al includes a small subset of Yasminelle and YAZ users. INAS-OC was a post-approval commitment to the FDA and EMA to investigate the safety of the 24-day regimen of DRSP 3 mg/ EE 0.02 mg (YAZ) in both the US (as a postmarketing safety study) and Europe (as a Post-Authorization Safety Study). The subjects in INAS represent an entirely new cohort from the previously-completed EURAS study.

The study has provided early information and regular updates on relevant clinical outcomes which has contributed to a continuous risk-benefit assessment during long-term follow up (3 to 5 years in the US, 2 to 4 years in Europe).

In the 2011 BMJ publication by Lidegaard et al, the authors also present data on DRSP-containing COCs with 0.02 mg EE, namely Yasminelle and YAZ, without distinguishing the cohort further by regimen (ie, 21 days for Yasminelle vs. 24 days for YAZ). It is therefore unclear from the paper how many YAZ users were actually included in the analysis. Yasminelle was launched in Denmark in October 2006 and YAZ in October 2008. Overall, the exposure for the total group in this cohort is limited with a total of 23,059 WY of exposure compared to 286,862 WY for Yasmin. In this cohort, 23 events were reported. The adjusted relative risk compared to no use is 4.84 with very wide CI of 3.19 to 7.33, pointing to the lack of robustness of this particular subanalysis.

While there could be some source of support to combine all DRSP-containing COCs, there are several clinically relevant differences between Yasmin and YAZ: the most obvious is the difference in EE dosage (0.03 mg for Yasmin, 0.02 mg for YAZ), the active days of treatment (21 days for Yasmin, 24 days for YAZ), and the additional indications for YAZ. These factors may drive a number of differences in terms of patient selection, including risk factors at baseline, duration and pattern of use, use of concomitant medications and co-morbidities. All of these elements of uncertainty were key factors in the alignment, from the time of approval, between the FDA, the EMA, and the sponsor, to conduct a separate study focusing on the risk of VTE with YAZ.

4.8.1.1 INAS-OC (unpublished)

Table 4-24: Structured Summary of Study Design as Reported by the Investigators for VTE - INAS

INAS, Dinger et al. (unpublished; data from 10 th study report, study status as of Feb 28, 2011)	
METHOD	
Objectives	To assess the risk of short and long-term use of YAZ and of established OCs in a study population that is representative of the actual users of the individual preparations.
Study Design	Observational cohort study – prospective
Geography	USA and EU (Austria, Germany, Italy, Poland, Sweden and UK)
Time Period	Start August 2005 (ongoing)
Population / Source of Data	Network of physicians who prescribe OCs at participating centers in the US and EU. All women who received a prescription for a new OC were asked by their physician if they were willing to participate. All women who consented to participate and who were either starters (first-ever users) or switchers were enrolled.
Sample size	Recruitment was completed in both US and EU (status Feb 28, 2011) A total of 85,260 women were recruited (of that US: 52,218) DRSP24d (YAZ): 15,561 DRSP21d: 9,401 Other OCs: 60,298 The follow-up time is 2-4 years, and the expected total observation time is > 200,000 WY.
ASSIGNMENT	
Baseline exclusion criteria	Clinicians chose COC use based on their clinical judgment. No other specific medical inclusion or exclusion criteria were applied.
Assessment of COC use	Patient questionnaire (self-administered). User groups divided according to: New users, who are first ever users or switchers
Comparator	1. LNG COCs 2. All other OCs (including LNG COCs)
Approach to achieving balance among groups	Risk factors ascertained via self-administered patient questionnaire. Adjustment for predefined confounding variables age, BMI, duration and pattern of use, and VTE history

ASSESSMENT	
VTE Definition	Initial detection based on twice yearly, patient completed questionnaire; Events confirmed by diagnostic measures with high specificity (eg, DVT: phlebography, duplex sonography; PE: pulmonary angiography, ventilation-perfusion scan, and spiral computed tomography). Events were classified as probable in absence of confirmation by an imaging test, but a clinical diagnosis is confirmed by a health professional or is supported by a non-imaging test (such as US doppler, plethysmography, D-dimer for VTE or typical ECG/blood gas tests for PE. These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis or long-term anticoagulant therapy). However, if the attending physician confirms that the diagnosis is correct, the event is classified as a VTE, even if a specific treatment was not given. Diagnosis excluded if diagnostic measures excluded the diagnosis, different medical condition diagnosed by a physician, or if no medical attention sought by subject. Process includes fatal cases.
VTE Validation Process	After patient-physician interviews, clinical chart review by 3 treatment-blinded adjudicators. VTE was deemed confirmed if at least 1 adjudicator considered the event as confirmed.

RESULTS
Study ongoing; Interim results (as of Feb 28, 2011): total 105 confirmed VTEs; Incidence rates (n): DRSP 24d: 7.6 / 10,000 WY (15) Other OCs: 8.1 / 10,000 WY (64)
INTERPRETATION / Authors' Overall Conclusion
Risk of VTE in Yasmin users is similar to those associated with the use of other OCs.

KEY FACTOR	APPROACH
Duration of use/ Pattern of use	Groups analyzed based specifically on duration of use and pattern of use
Attrition of susceptibles/ Healthy user effect	Analysis by groups based on history of prior use, including first-time ever use cohort
Prescription bias	Key risk factors ascertained by questionnaire at baseline and updated every 6 months / Analyses adjusted for risk factors
Validity of diagnosis For VTE	Medical records review / Adjudication by 3 exposure-blinded experts

Strengths:

- Community-based observational study which mimics clinical practice, including the US
- Ascertainment of events through a self-administered questionnaire administered every six months, documenting exposure and AEs
- Balance achieved by accounting for predefined confounding factors such as age, BMI, history (personal and family) of VTE
- Separate and pre-planned subanalyses based on duration and pattern of use, including first-time ever use; the time-dependent decline of the VTE incidence was similar for all OCs.
- VTE cases confirmed through clinical records review, and adjudication by 3 exposure-blinded experts
- Multi-step algorithm for patient follow-up, including search of governmental records for deaths to ensure all events were captured

Limitations:

- VTEs are self-reported by the study subjects. External environment may drive increased awareness of the risk of VTE with Yasmin, and lead to a referral/diagnostic bias
- Diagnosis of VTE is based on local clinical standards, without a pre-specified diagnostic algorithm. Some diagnostic methods for VTE (eg, D-dimer) are known to be poorly reliable. This may have introduced a non-differential classification bias (validation of diagnosis) that may have reduced the likelihood of finding a difference between the groups observed.

With regard to the issue of a differential risk of VTE for DRSP-containing COCs, the retrospective studies either encompassed a time period when YAZ was not yet approved, or fail to specifically point out any data that applies to YAZ. All interim results from the INAS-OC study, submitted to the FDA and other regulatory authorities, indicate that the risk of VTE with YAZ is similar to that of the other COCs studied, including LNG-containing COCs.

The sponsor reaffirms that, based on the best available scientific evidence, the risk of developing VTE or blood clots in women using YAZ is comparable to other combination birth control pills studied, including those containing LNG.

5. Mechanism of action - chemistry and preclinical data

Since their introduction in the 1960s, all COCs contained progestins derived from 19-nortestosterone. None of these synthetic progestins, however, have demonstrated the antimineralocorticoid activity of endogenous progesterone. Both E2 and EE promote mineralocorticoid activity by stimulating the renin-angiotensin-aldosterone system (RAAS) leading to increased sodium and water retention. As a consequence, even low-dose COCs have the potential to lead to sodium and fluid retention, manifesting clinically as breast tenderness, edema, transient weight gain, and elevated blood pressure in susceptible women.

In this context, research was aimed at the development of a COC containing a low dose of EE that could be combined with a progestin with a pharmacodynamic profile similar to that of progesterone. During the search for new substances, DRSP was synthesized.

DRSP is a progestin that differs from all other progestins currently available in that it is a derivative from 17-spirolactone and not from 19-nortestosterone or 17 α -hydroxyprogesterone. Like natural progesterone, DRSP possesses progestogenic and antimineralocorticoid properties. In addition, it has antiandrogenic properties. It is devoid of any direct androgenic, estrogenic, or glucocorticoid activity.

In in-vitro and in-vivo preclinical models, DRSP exhibits potent progestational, antimineralocorticoid and antiandrogenic activity. In comparison to other progestins, the pharmacological profile of DRSP is closest to progesterone ([Table 5-1](#)).

Table 5-1: Pharmacological Profiles of Selected Progestins in Animal Models

	Progestogenic activity	Androgenic activity	Antiandrogenic activity	Antimineralocorticoid activity
Progesterone	+	-	(+)	+
Drospirenone	+	-	+	+
<i>Desogestrel</i>	+	(+)	-	-
<i>Levonorgestrel</i>	+	(+)	-	-
<i>Norgestimate</i>	+	(+)	-	-
<i>Norethisterone</i>	+	+	-	-

(+) indicates negligible at therapeutic dosages, - no effect, + distinct effect

Progestins in italics are all derived from 19-nortestosterone

([Krattenmacher, 2000](#); [Schindler et al., 2003](#))

The other component of Yasmin is the estrogen EE, the most widely used estrogen in COCs. On its own, EE binds with high affinity to the estrogen receptor but minimally to the progesterone and the glucocorticoid receptors, and not at all to the androgen receptor.

The properties of EE as the estrogen component of COCs has been well established through in-vitro and in-vivo preclinical models.

Studies were conducted to examine the possible drug-drug interaction of EE in the binding affinity of DRSP. EE does not interfere with the interaction of DRSP with the progesterone receptor. Similarly, EE does not interfere with the antimineralocorticoid action of DRSP.

The preclinical data available support the differentiated nature of DRSP as a progestin. DRSP is an active progestin, with antimineralocorticoid and antiandrogenic activity. It does not display any significant in-vivo or in-vitro androgenic, estrogenic, glucocorticoid or antiglyucocorticoid activity. DRSP has been the subject of an extensive non-clinical safety program and its non-clinical profile has been thoroughly characterized. The results do not yield any specific safety concern distinct from the broad class of progestins.

Based on the chemistry and preclinical data, the goal of developing a potent oral progestin which displays both the progestational and antimineralocorticoid activities of natural progesterone was achieved with DRSP.

6. Yasmin / Safyral (generics: Ocella)

Based on the preclinical information outlined in [Section 5](#), the clinical development of DRSP/EE based COCs was undertaken. The program progressed and ultimately resulted in the approval of the first DRSP-containing COC, Yasmin. Key elements of the clinical development program, and the overall clinical profile of Yasmin, are outlined below.

6.1 Clinical development

6.1.1 Clinical pharmacology

DRSP was investigated in over 40 Clinical Pharmacology studies with either DRSP alone, different DRSP/EE combinations or – in some specific drug-drug interaction studies or special population studies – DRSP in combination with E2. Overall, over 1000 young, healthy women participated in these studies.

This section summarizes the clinical pharmacokinetic and pharmacodynamic properties of DRSP as the progestin of Yasmin and Safyral (the levomefolate-supplemented version of Yasmin).

Systemic exposure:

DRSP is rapidly absorbed following oral administration with peak plasma concentration attained around 1-2 h post dosing. DRSP has high oral bioavailability (76-85%) which contributes to a reliable, reproducible systemic exposure. DRSP concentrations decrease in serum with a terminal half-life of approximately 30 h leading to less fluctuation of plasma DRSP levels and is assumed to improve contraceptive efficacy with regard to dosing errors (see [Section 7](#)).

In line with the observed half-life, there was a 2-3 fold accumulation in serum C_{max} and AUC(0-24h) values of DRSP following multiple-dose administration of Yasmin. Steady-state DRSP plasma concentrations were observed after 8 days of daily dosing. The linearity index of DRSP in combination with EE (determined as the ratio of AUC(0-24h) at steady-state divided by the AUC after single dose) varied between 0.8 and 1.6. Systemic DRSP exposure increases proportionally with increasing doses, indicating linear pharmacokinetics with respect to dose.

Pharmacokinetic drug interaction:

Due to its multiple elimination pathways (extensive metabolism catalyzed by several enzymes as well as renal and hepatic excretion mainly as metabolites) and no cytochrome P450 system involvement in main metabolic pathways, DRSP has a limited potential for pharmacokinetic drug-drug interactions. As no pharmacokinetic drug-drug interaction between levomefolate calcium and DRSP/EE has been identified in single-dose bioequivalence studies, the safety and efficacy data relating to DRSP and EE following administration of Yasmin/YAZ are applicable to Safyral and Beyaz.

Antimineralocorticoid activity:

DRSP/EE combinations cause an increase in plasma renin activity and plasma aldosterone induced by DRSP's mild antimineralocorticoid activity. DRSP intake did not show an effect on the serum potassium concentration in healthy women and in patients with mild or moderate renal impairment. However, a potential for hyperkalemia was concluded for patients with mild or moderate renal impairment and pretreatment potassium levels in the upper normal range who are additionally using potassium sparing drugs. In further clinical studies, treatment with Yasmin and YAZ was not associated with an increased risk of hyperkalemia (see [Section 4.8.1](#)). The topic was specifically addressed in a large prospective, observational study where no evidence of an increased rate of hyperkalemia or complications of hyperkalemia among Yasmin initiators compared to other OC initiators was observed. ([Loughlin et al., 2008](#))

In conclusion, DRSP, administered alone or in combination with EE, has a predictable and well-reproducible pharmacokinetic and pharmacodynamic profile.

6.1.2 Efficacy in clinical trials**6.1.2.1 Efficacy results – contraception****6.1.2.1.1 Overview**

Efficacy parameters for Yasmin, which were studied and submitted as part of NDA 21-098 and submitted in 1999, included contraceptive effectiveness and cycle control. The data are derived from 2 pivotal multicenter, open-label studies of efficacy and safety, the customary approach for the development of COCs, and 8 supportive studies.

The studies comprised 3802 subjects overall: 3476 in Europe and 326 in the US. The efficacy data discussed here is restricted to the population that received Yasmin or a DSG-containing COC (0.150 mg/EE 0.30 mg) (939 subjects) ([Table 6-1](#)).

Table 6-1: Studies Included in the Assessment of Efficacy

Report/Study Number	Study	Study Design	Completed Cycles	Study Medication	Number of Subjects	Mean Age in Years / Age Range
Pivotal Studies						
AI51/92052	Efficacy/Safety Phase 3	Open-labeled, Randomized, Multicenter	26	DRSP 3 mg/EE 0.03mg DSG 0.150 mg/EE 0.03 mg	442 445	26.5
98180/96049	Efficacy/Safety Phase 3	Multicenter	13	DRSP 3 mg/EE 0.03mg	326	26.4
Supportive Studies						
AJ06/93044	Efficacy/Safety Phase 3	Open-labeled, Randomized, Multicenter	13	DRSP 3 mg/EE 0.03mg DSG 0.150 mg/EE 0.03 mg	1657 412	25.2
A187/90031	Efficacy/Safety Phase 2	Double-blind, Randomized, Multicenter	6	DRSP 3 mg/EE 0.03mg DRSP 3 mg/EE 0.02mg DRSP 3 mg/EE 0.015mg LNG 0.150 mg/EE 0.03 mg	49 50 50 49	18-37
AE91/92038	Hemostasis Phase 3	Open-label, Randomized; Single Center	6	DRSP 3 mg/EE 0.03mg DRSP 3 mg/EE 0.02mg DSG 0.150 mg/EE 0.03 mg	25 25 25	22.4 24.5
AG44/92083	Hemostasis/RAAS Phase 3	Open-label, Randomized; Single Center	13	DRSP 3 mg/EE 0.03mg DSG 0.150 mg/EE 0.03 mg	30 30	23.9
AL84/93050	Lipids/Carbohydrate Metabolism, Phase 3	Open-label, Randomized; Single Center	13	DRSP 3 mg/EE 0.03mg DSG 0.150 mg/EE 0.03 mg	27 27	21.4
AM90/94151	Endometrium	Multicenter, Open-Label, Non-Comparative	13	DRSP 3 mg/EE 0.03mg	40	27.6
9970/90030	RAAS, Electrolyte, Lipid and Carbohydrate Metabolism	Double-blind, Randomized, Single-Center	6	DRSP 3 mg/EE 0.03mg DRSP 3 mg/EE 0.02mg DRSP 3 mg/EE 0.015mg LNG 0.150 mg/EE 0.03 mg	20 20 20 20	18-34
AI98/93026	Long Term, Pharmacokinetics	Open-Label, Not Randomized, Single Group, Multi-Dose	13	DRSP 3 mg/EE 0.03mg	13	18-35

Reference: NDA 21-098, Integrated Summary of Efficacy, Text table 1.

6.1.2.1.2 Results of contraceptive efficacy

Contraceptive efficacy was determined through the well-established Pearl Index (PI) calculations (corrected and uncorrected⁵). The Pearl Index represents the number of pregnancies documented among the equivalent of 100 woman-years. The corrected PI was based on the total number of completed cycles in which no back-up contraceptive methods were used: 33,160 cycles for Yasmin and 15,061 cycles for DSG/EE. The PI for YAZ was calculated differently than the PI calculated for Yasmin due to the evolution of assessment methodologies.

Considering all subjects in the pivotal studies, 4 pregnancies occurred on Yasmin and 3 pregnancies occurred on DSG 0.150 mg/EE 0.30 mg. The corrected PIs for DRSP/EE and DSG/EE in the pivotal studies were both 0.41.

Considering all subjects across all contraception trials, 14 pregnancies occurred on Yasmin and 5 pregnancies occurred on DSG 0.150 mg/EE 0.30 mg. The corrected PIs for DRSP/EE and DSG/EE were 0.55 and 0.43, respectively (Table 6-2).

Table 6-2: Assessment of Contraceptive Efficacy in All Efficacy Studies

	All Subjects	
	DRSP/EE (N = 2629)	DSG/EE (N = 939)
Number of pregnancies	14	5
Total cycles ^a	33549	15206
Cycles without other contraception ^b	33160	15061
Uncorrected Pearl Index ^c	0.54	0.43
Corrected Pearl Index ^d	0.55	0.43

N = total number of subjects in the specific treatment group.

^a All cycles in which at least 1 tablet was taken.

^b All cycles in which at least 1 tablet was taken and in which no condom was documented

^c Uncorrected Pearl Index = (Pregnancies * 13 *100)/ Total complete cycles

^d Corrected Pearl Index = (Pregnancies * 13 *100)/ Total complete cycles without other contraception

6.1.3 Postmarketing efficacy studies

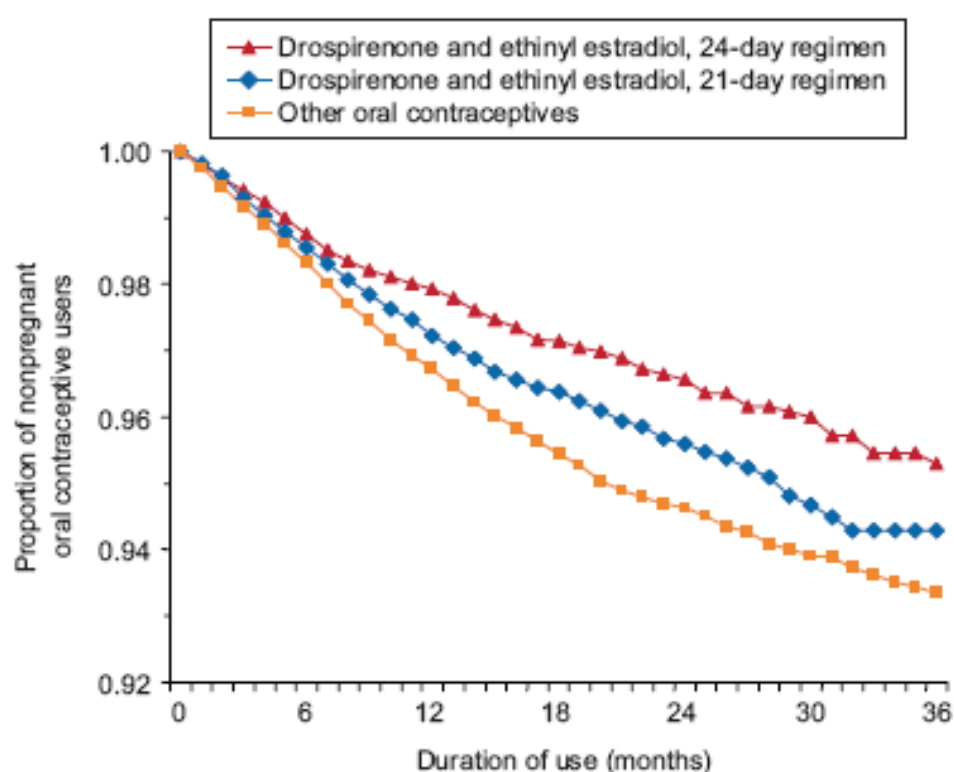
6.1.3.1 INAS efficacy data

The INAS study (see Section 4.8.1 above) includes a pre-specified secondary objective to estimate real-life effectiveness of OC pills by the progestin in each COC, the length of pill-free interval in the COC regimen (7 days vs. 4 days vs. none), and BMI. Outcome

⁵ Contraceptive effectiveness was assessed by the Pearl Index both uncorrected and corrected for cycles in which an additional contraceptive method was used. All cycles were admitted into the calculation of the Pearl Index regardless of how many tablets were taken during any given cycle.

data from the 52,218 US participants in the INAS study have been reported (Dinger et al., 2011). The authors of the study concluded that DRSP in a 24-day regimen, as found in YAZ, was associated with the lowest contraceptive failure rates among the COCs studied. In a comparison of the 24- and 21-day regimens of DRSP to other OCs, the corresponding results for the three cohorts evaluated were 2.1% for DRSP/EE 24d, 2.8% for DRSP/EE 21d, and 3.5% for other OCs after the first year of OC use (Figure 6-1 and Table 6-3).

Figure 6-1: Life-Table Estimates of Contraceptive Failure Associated With the Use of 24-Day Regimens of DRSP and EE, 21-Day Regimens of DRSP and EE, and Other Oral Contraceptive Pills



Reference: Dinger. Real-life oral contraceptive pill effectiveness. *Obstet Gynecol* 2011;117:33-40, Figure 3.

Table 6-3: Life-Table Estimates of the Rate of Contraceptive Failure After 1, 2, and 3 Years of Oral Contraceptive Use

Cohort	Contraceptive Failure (%) at the End of Year		
	1	2	3
DRSP/EE _{24d}	2.1 (1.7–2.4)	3.4 (2.9–4.0)	4.7 (3.8–5.6)
DRSP/EE _{21d}	2.8 (2.2–3.3)	4.5 (3.6–5.4)	5.7 (4.5–6.9)
Other OC	3.5 (3.3–3.7)	5.4 (5.1–5.7)	6.7 (6.2–7.1)

DRSP, drospirenone; EE, ethinyl E₂; OC, oral contraceptive.
Data presented as point estimates (95% confidence intervals).

Reference: Dinger. Real-life oral contraceptive pill effectiveness. *Obstet Gynecol* 2011;117:33-40, Table 2.

The finding that contraceptive effectiveness for a 21-day regimen of DRSP is intermediate between that of a 24-day regimen containing it and other OCs (with other progestins in mostly 21-day regimens) supports that the longer half-life of DRSP may have a clinically meaningful impact and difference relative to other 21-day OC regimens with a progestogen that has a shorter half-life under conditions of imperfect or typical use.

6.1.4 Safety in clinical trials

A total of 16 clinical studies provide information on the tolerability and safety of Yasmin and Yasmin combined with Metafolin (approved in the US with the tradename Safyral). Among them are 13 studies with Yasmin as an OC, 2 studies to investigate the use of Yasmin in the treatment of PMS and PMDD, and 1 study to investigate Safyral on folate status (see [Table 6-4](#)).

Table 6-4: Overview of Clinical Studies Providing Information on Tolerability and Safety of Yasmin and Yasmin + Metafolin

Study no. (protocol no.)	Phase	Main objective (short title)	Duration	Treatment groups No. of women (FAS)
OC studies				
A151 (92052)	3	Pearl Index and cycle control	26 cycles	Yasmin: 442 Marvelon: 445
AJ06 (93044)	3	Pearl Index and cycle control	13 cycles	Yasmin: 1,657 Marvelon: 412
98180 (96049B)	3	Pearl Index	13 cycles	Yasmin: 326
A187 (90031)	2	Pearl Index and cycle control	6 cycles	Yasmin: 49 DRSP/EE 3/0.02: 50 DRSP/EE 3/0.015: 50 Microgynon: 49
AE91 (92038)	3	Hemostasis	6 cycles	Yasmin: 25 DRSP/EE 3/0.02: 25 Microgynon: 25
AG44 (92083)	3	Hemostasis, RAAS	13 cycles	Yasmin: 30 Marvelon: 30
9970 (90030)	2	RAAS, metabolism	6 cycles	Yasmin: 20 DRSP/EE 3/0.02: 20 DRSP/EE 3/0.015: 20 Microgynon: 20
AL84 (93050)	3	Metabolism	13 cycles	Yasmin: 27 Marvelon: 27
AM90 (94051)	3	Endometrium	13 cycles	Yasmin: 40
AI98 (93026)	3	Long term PK	13 cycles	Yasmin: 13
AI99 (93027)	3	DRSP PK in serum & breast milk	8 months	Yasmin: 9
9693 (89099)	2	PD comparison	3 cycles	Yasmin: 26 DRSP 2 mg + EE 0.03 mg: 26
9692/A470 (89110)	2	RAAS, electrolyte metabolism	3 cycles	Yasmin: 35 DRSP 2 mg + EE 0.03 mg: 35
PMS and PMDD studies				
AM91 (94160) NDA 21-098	3	PMS	3 cycles	Yasmin: 28 Microgynon: 29
A01438 (97036D) NDA 21-098	3	PMS, PMDD	6 cycles	Yasmin: 129 Placebo: 130

(continued)

Table 6-4: Overview of Clinical Studies Providing Information on Tolerability and Safety of Yasmin and Yasmin + Metafolin (continued)

Study no. (protocol no.)	Phase	Main objective (short title)	Duration	Treatment groups No. of women (FAS)
Folate study				
A39814 (309763)	1	Folate status	6 cycles with either Yasmin +Metafolin or Yasmin + FA ; follow-up of 5 cycles with Yasmin only	Safyral/Yasmin: 86 Yasmin + FA/ Yasmin: 86

6.1.4.1 Results

6.1.4.1.1 Study population for the safety assessment

Exposure

Based on the clinical studies included to investigate the tolerability and safety of Yasmin as an OC and in the PMS/PMDD and folate studies, a total of 4,421 women were included in the overall safety assessment, among them 2,856 women treated with Yasmin, 86 with Safyral followed by Yasmin, 86 with Yasmin + folic acid followed by Yasmin, 95 with DRSP/EE 3/0.02, 61 women with DRSP 2 mg/EE 0.03 mg, 70 women with DRSP/EE 3/0.015, 123 with Microgynon, 914 with Marvelon, and 130 with placebo.

6.1.4.1.2 Medically relevant adverse events with respect to Yasmin

In the course of the clinical development program of Yasmin, particular attention was paid to AEs considered to be medically relevant to hormonal contraceptive use, including VTEs.

In accordance with the CPMP Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Diseases (CPMP/EWP/563/98), DVT and PE were considered to be cases of VTEs, but cases of superficial thrombophlebitis were not included. VTEs were recorded for 1 of 2,699 women treated with Yasmin in the OC studies. The event of PE (severe) was reported in study AI51. This case was considered to be an adverse drug reaction and led to discontinuation of study drug. Additionally, the PE was classified as a SAE.

No cases of VTE were reported among the 157 women treated with Yasmin in the PMS/PMDD studies.

Safyral:

No cases of VTE were reported among the 172 women treated with either Safyral followed by Yasmin or Yasmin + folic acid followed by Yasmin in the folate study.

In summary, the exposure of women treated with Yasmin or Safyral in clinical studies is too limited to adequately quantify the risk of rare events such as VTE. Nevertheless, the findings observed for Yasmin were in line with the safety profile of other COCs.

6.1.4.1.3 Clinical laboratory evaluations

General safety laboratory evaluations from the OC studies included parameters of hematology, serum chemistry, liver, renal and pancreatic enzymes and urinalysis. Irrespective of whether the pooled database or results from the individual studies were considered, the overall levels of the general laboratory variables were unaffected by Yasmin. The majority of women treated with Yasmin had normal parameters of hematology, serum chemistry, liver, renal and pancreatic enzymes and urinalysis at baseline and post-baseline. Individual laboratory abnormalities did not give rise to any safety concerns. No trends indicating clinically relevant changes in laboratory parameters were observed. Treatment with Yasmin was not found to be associated with an increased risk of hyperkalemia. Thus, the safety of Yasmin with respect to laboratory evaluations was demonstrated.

6.1.4.2 Safety conclusion in clinical trials

The safety of Yasmin/Safyral is well established. On the basis of the Full Analysis Set (FAS) of the various clinical development programs, which comprised 2,699 women from the clinical studies to investigate Yasmin as an OC, 157 women from PMS/PMDD studies, and 86 women treated with Safyral followed by Yasmin and 86 women treated with Yasmin + folic acid followed by Yasmin from the clinical study that investigated folate status, the safety findings for Yasmin did not give rise to any new safety concerns compared to the side effect profile of other COCs.

6.1.5 Benefit-risk profile of Yasmin

Yasmin is a 21/7 COC regimen with 3.0 mg of DRSP and 0.03 mg of EE, a progestin that displays unique antimineralocorticoid properties. Yasmin has undergone a comprehensive development program, relative to its initial US approval in 2001. The accumulated scientific evidence continues to demonstrate that Yasmin is an effective form of contraception. The Yasmin label provides guidance about managing the unique antimineralocorticoid properties of DRSP, and no increased incidence of AEs related to this aspect of the Yasmin label have been identified. When used in accordance with the product labeling, the risk profile for Yasmin is aligned with the class label for COCs.

With respect to the risk of VTE, the current class label (PLR format) for all approved COC formulations reflect a risk in the range of 3-9 per 10,000 WY for COC users, with the risk being highest during the first year of use. With input and agreement from

regulatory authorities, the sponsor commissioned two prospective studies, EURAS and Ingenix, which were conducted by independent research organizations to evaluate the risk of VTEs associated with the use of Yasmin and to compare that risk to other COCs. Both studies concluded that the risk of VTE in Yasmin users was comparable to that seen with other COCs, including those containing LNG.

Since 2009, however, the results of four retrospective database studies have been published, reporting a higher risk of VTE in Yasmin users compared to those on COCs using LNG. The current briefing document provides a comprehensive integrated analysis of the available data, along with a review of the methodological differences and the comparative strengths and weaknesses of the prospective and the retrospective studies. This analysis supports the conclusion that the risk of VTE in Yasmin users is comparable to that seen with other COCs, including those containing LNG.

In summary, the overall benefit-risk profile of Yasmin (and Safyral) is favorable and aligns with the general class of COCs, including LNG-containing COCs, when used in accordance with the product labeling.

7. YAZ / Beyaz (generics: Gianvi)

The development of YAZ with its 24-day regimen aimed at improving contraceptive reliability via stronger ovarian suppression and reduced fluctuation of sex hormones.

The high doses of EE and progestin in early OCs were associated with side effects, including nausea, breast tenderness, and weight gain, that adversely affected patient compliance. As a result, the dose of EE has been reduced from the original 0.150 mg to 0.015 - 0.035 mg per day. The half-life of EE is constant at any dose, however, at the lower doses used in newer OCs, EE clears from the circulation 2 to 3 days after the active pill has been discontinued, allowing several hormone-free days in which FSH levels rise and follicular growth occurs. The growing follicles start to produce estradiol, but once EE in the OC is re-administered, FSH levels are suppressed and further follicular growth is inhibited. The incidence of follicular growth during the hormone-free interval has been shown to be greater with OCs containing 0.02 mg EE than with higher doses. The development of newer, more potent progestins has allowed the use of lower doses of EE in current OCs.

As with the estrogen component, progestins are cleared from the circulation within a few days of stopping the active pill, allowing LH levels to rise. Therefore, ovulation may occur if the new cycle of active pills is not started exactly 7 days after the last active pill was taken. Creinin et al. found that extending the hormone-free interval from 7 to 9 days with two low-dose formulations resulted in some women having elevated circulating endogenous progesterone levels, which is evidence of luteal activity ([Creinin et al., 2002](#)). Only about 1% of women whose OC use is monitored as part of a clinical trial become pregnant. In contrast, an estimated 8% of US women become pregnant during the first year of OC use. This discrepancy is believed to be due, at least in part, to women who inadvertently extend the hormone-free interval by failing to start their new pill pack on schedule, increasing the likelihood of a developing follicle to ovulate.

Decreasing the hormone-free interval from 7 to 4 days should allow for sufficient level of hormones in the circulation at the time the new cycle of active pills is begun, resulting in continual suppression of LH and FSH levels and prevention of follicular growth during the hormone-free interval. Continued inhibition of follicular development throughout each month of OC use should decrease the incidence of ovulation and pregnancy with typical use due to failure to begin taking the active pills on schedule. Meanwhile, data of the ongoing INAS study, a large, prospective, comparative cohort-study, have substantiated that the contraceptive effectiveness of YAZ under real-life conditions is superior to other OCs including Yasmin (see [Section 4.8.1](#) above). Robust evidence for a clinically meaningful contraceptive benefit for YAZ users compared to users of other OCs is provided.

7.1 Clinical development

7.1.1 Clinical pharmacology

YAZ and Beyaz (the levomefolate-supplemented version of YAZ) are low EE dose formulations of Yasmin and Safyral. The hormone containing tablets of these products are administered in a 24 day regimen instead of the traditional regimen of 21 day as for Yasmin and Safyral.

The lower administered EE dose (0.02 mg EE) results in a proportional lower systemic EE exposure following single and multiple dosing of YAZ/Beyaz as compared to Yasmin/Safyral (0.03 mg EE). As anticipated, the 24-day regimen of YAZ/Beyaz lead to a stronger suppression of follicular development compared to the 21-day regimen. This was demonstrated in a study comparing both regimens and mimicking a real-life situation by the introduction of intentional dosing errors. (Klipping et al., 2008)

7.1.2 Efficacy in clinical trials

7.1.2.1 Clinical efficacy – oral contraception

Proof of the contraceptive efficacy of YAZ is based on the low number of pregnancies in 2 phase 3 clinical studies submitted as part of NDA 21-676 (pivotal studies A12007 and supportive study A09151) (Table 7-1). The contraceptive reliability was analyzed using two different methods: the PI and a life-table analysis. YAZ was approved for oral contraception in March 2006. The PI for YAZ was calculated differently than the PI calculated for Yasmin due to the evolution of assessment methodologies.

Table 7-1: Summary of Studies Providing Contraceptive Efficacy Data

Report/ Protocol Number	Study Type Phase	Study Design	Study Medication	Duration of Treatment (regimen)	Number of Subjects Treated	Age Range in Years (Mean)
Pivotal Study						
A12007/ 303740	Efficacy/Safety Phase 3	Multicenter, uncontrolled, open-label	DRSP 3 mg + EE 0.02 mg	13 cycles (24-day regimen)	1027	17-36 (24.7)
Supportive Study						
A09151/ 301888	Lipid, hemostatic, carbohydrate metabolism/ Safety Phase 3	Single- center, randomized, open-label	DRSP 3 mg + EE 0.02 mg	7 cycles (24-day regimen)	29	18-35 (23.8)
			Mercilon®	7 cycles (21-day regimen)	30	18-34 (23.7)

DRSP = drospirenone; EE = ethinyl estradiol; Mercilon® = 0.150 mg desogestrel + 0.02 mg EE.

Results:

The pivotal efficacy study (Report A12007) was an uncontrolled, multicenter, open-label study of efficacy and safety of YAZ. Women 17 to 36 years of age who were in good general health and requested contraceptive protection were recruited. A total of 1027 women received study drug in a 24-day regimen for 13 cycles. The PI was the primary criterion to assess contraceptive reliability. It was assessed assuming that all subjects were at risk for pregnancy in all medication cycles unless back-up contraception, medication with contraceptive side effect, or any other reason that reduced the chance of conception was documented. The study collected data from 11,140 cycles under treatment.⁶

The PI in study A12007, calculated on the basis of 11 pregnancies observed during treatment for the pivotal study, was 1.29 with an upper 97.5% confidence limit of 2.30. The PI was based on the total number of completed cycles in which no back-up contraceptive methods were used: Results from this pivotal efficacy study, including both PI and Kaplan-Meier survival analysis, showed that DRSP 3 mg/ EE 0.02 mg was effective as a contraceptive and provided good cycle control.([Bachmann et al., 2004](#))

The supportive study (Report A09151) was a single-center, open-label, randomized study to investigate the effect of YAZ on plasma lipids, hemostatic variables, and carbohydrate metabolism compared with a 21-day regimen of Mercilon[®]. A total of 59 women (29 women treated with YAZ) were treated for 7 cycles. In addition to these parameters, bleeding patterns and pregnancy data were collected. Both treatments were safe and efficacious with good cycle control and contraceptive reliability.

No pregnancies were reported during treatment with YAZ in Report A09151.

7.1.2.2 Clinical efficacy – PMDD

The clinical development program of YAZ in the treatment of symptoms of PMDD was based on two pivotal clinical phase 3 studies Submitted as part of NDA 21-873 (studies A21566 [parallel group design] and A07545 [crossover group design], [Table 7-2](#)). Both studies were performed in the US. The 24 day regimen of YAZ was considered to be especially suited to treat symptoms of PMDD since it extends the benefits of the antimineralocorticoid and antiandrogenic properties of DRSP into the most symptomatic time of the cycles of women suffering from PMDD. YAZ was approved for the treatment of PMDD in women who choose an OC for contraception in October 2006.

Multiple questionnaires completed by either the subject or the investigator were used to evaluate the effectiveness of DRSP/EE and placebo treatment on the symptoms of PMDD. The main questionnaire utilized was the Daily Record of Severity of Problems scale

⁶ Cycles that were considered noncompliant or where back-up contraception was used were excluded. A treatment cycle was defined to be compliant if all 28 pills were taken on 30 successive days. The corrected Pearl Index (PIc) was assessed accounting for method failures. A pregnancy was considered as a method failure if the estimated day of conception was in a compliant cycle and a method failure could not be excluded on the basis of the comments on the pregnancy report form.

(Endicott, 1997), in which changes to the score of the first 21 items in the scale, consisting of mood and physical symptoms, comprised the primary efficacy variable for both studies. The remaining three items—referred to as the functional impairment items—relating to decreased productivity and interference in each social activities and relationships were assessed as a secondary efficacy variable.

Table 7-2 Clinical Development Program: Overview of Clinical Studies to Evaluate the Efficacy of YAZ in the Treatment of PMDD

Report/ Protocol Number	Study Type Phase	Study Design	Study Medication	Duration of Treatment (regimen)	Number of Subjects Treated	Age Range in Years (Mean)
Pivotal efficacy studies						
A21566/ 304049	Efficacy/ Safety Phase 3	Multicenter, randomized, double blind, placebo- controlled, parallel	DRSP/EE	3 cycles (24-day regimen)	231	18-40 (31.0)
			Placebo		218	18-42 (32.0)
A07545/ 305141	Efficacy/ Safety Phase 3	Multicenter, randomized, double blind, placebo- controlled, crossover	DRSP/EE; Placebo ^a	6 cycles (24-day regimen)	34	19-39 (31.0)
			Placebo; DRSP/EE ^b		30	20-40 (33.0)

DRSP = drospirenone; EE = ethinyl estradiol; DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg.

^a Treatment group first received DRSP/EE for 3 treatment cycles, then no study medication for 1 cycle, and then placebo for 3 treatment cycles.

^b Treatment group first received placebo for 3 treatment cycles, then no study medication for 1 cycle, and then DRSP/EE for 3 treatment cycles.

Results:

Pivotal Study A21566

Study A21566 was a multicenter, randomized, double-blind, parallel group study which evaluated the safety and efficacy of YAZ in treating the symptoms of PMDD in 77 US centers, of which 64 sites randomized subjects to study drug. The study was composed of 2 phases: the qualification phase consisted of 2 run-in (menstrual) cycles, and the treatment phase consisted of 3 treatment cycles with YAZ or placebo. Results of this study were also published (Yonkers et al., 2005).

The primary efficacy variable was the Daily Record of Severity of Problems scale, recorded daily during the study, rating the individual items (ie, symptoms) on a scale of 1 (not at all) to 6 (extreme). A decrease in scores indicates improvement in symptoms.

For treatment with YAZ, the mean change from the baseline Daily Record of Severity of Problems score was -37.49. For treatment with placebo, the mean change from the baseline Daily Record of Severity of Problems score was -29.99. The difference between treatment groups (-7.500) was statistically significant ($p = 0.0001$).

Pivotal Study A07545

Study A07545 was a multicenter, randomized, double-blind, crossover group study which evaluated the safety and efficacy of YAZ in treating the symptoms of PMDD in 24 US centers, of which 17 randomized subjects to study drug. The study was composed of 2 phases: the qualification phase consisted of 2 run-in (menstrual) cycles, and the treatment phase consisted of 3 treatment cycles with YAZ or placebo (Treatment Period 1), 1 drug-free washout cycle, and 3 treatment cycles with the converse of the drug taken in the first period (Treatment Period 2). All subjects in the screening phase or who had been randomized to receive study medication as of November 2002 were followed to completion. Results of this study were also published ([Pearlstein et al., 2005](#)).

As with study A07545, the primary efficacy variable was the Daily Record of Severity of Problems scale. For treatment with YAZ, the mean change from the baseline Daily Record of Severity of Problems score was -22.94. For treatment with placebo, the mean change from the baseline Daily Record of Severity of Problems score was -10.46. The difference between treatments (-12.47) was statistically significant ($p = 0.0001$).

7.1.2.2.1 Further confirmatory data in literature

A literature review of the Biomedical Core Database was conducted in July 2011 for COC therapy of PMDD. For the combination of DRSP 3 mg and EE 0.2 mg (YAZ), the main publications that exist are related to the efficacy trials supporting its approval for PMDD—already cited in this document—or secondary analyses and review articles. An additional study was identified in which subjects who were non-OC users or users of an OC without DRSP were diagnosed via the Premenstrual Symptoms Screening Tool and then placed on or switched to YAZ ([Svojanovska, 2010](#)). Significant declines in the summary scores on the Premenstrual Symptoms Screening Tool were demonstrated in both groups after 3 or 4 months of YAZ use. Scores decreased from 24.9 to 8.2 in the previous non-OC users and from 24.3 to 6.0 in those who switched from other OCs. The author concluded that YAZ was effective in the treatment of severe PMS/PMDD and should be considered for therapy in individuals diagnosed with severe PMS/PMDD who wished to use an OC and who were either not using one or were on a different one.

YAZ is the only OC with an FDA-approved indication for the treatment of the physical and emotional symptoms of PMDD. An evaluation of Yasmin for PMDD, in which subjects were diagnosed by DSM-IV criteria as in the YAZ trials, compared it to placebo and demonstrated improvement in symptoms as assessed by the Calendar of Premenstrual Experiences scale ([Freeman et al., 2001](#)). Statistical significance in differences was only reached on one of the items, however. While many OCs have been evaluated—and exhibited variable effects—for reduction of physical and emotional symptoms associated with the menstrual cycle, none, including Yasmin and YAZ, have been shown to be effective for PMS, and no other OC has been shown to be effective for PMDD.

7.1.2.3 Clinical efficacy – acne vulgaris

The clinical development program of YAZ in the treatment of moderate acne vulgaris was based on two pivotal clinical phase 3 studies submitted as a supplement to NDA 21-676 (studies A25083 and A25152) (Table 7-3). Both studies were performed in the US. The results of these studies have been published (Anttila et al., 2011; Koltun et al., 2008; Lucky et al., 2008; Maloney et al., 2008, 2009). YAZ was approved for the treatment of moderate acne vulgaris in women who choose an OC for contraception in January 2007.

Table 7-3 Overview of Clinical Phase 3 Studies to Evaluate the Efficacy of YAZ in the Treatment of Moderate Acne Vulgaris

Study (protocol no.)	Indication / study design	Number of women by treatment group (amended FA set) ^a		Treatment duration
Pivotal efficacy studies				
A25083 (306820)	moderate acne vulgaris multicenter, double-blind, randomized, placebo-controlled	YAZ: 229 Placebo: 227		6 cycles
A25152 (306996)	moderate acne vulgaris multicenter, double-blind, randomized, placebo-controlled	YAZ: 222 Placebo: 215		6 cycles

^a Note: the number of women refers to the amended full analysis set (FAS): women had to have a minimum of 40 lesions, ie, at least 20 inflammatory lesions and at least 20 non-inflammatory lesions.

Results:

Studies A25083 and A25152 were multicenter, double-blind, randomized, placebo-controlled studies to evaluate the efficacy and safety of YAZ as an acne therapy in women with moderate acne vulgaris. The studies were identical with respect to their design and study course except for additional hormone measurements performed in study A25083. In each study, approximately 500 otherwise healthy women who met the inclusion criteria of a minimum of 40 lesions (ie, at least 20 inflammatory lesions and at least 20 non-inflammatory lesions), of reproductive age (14 to 45 years), and who required treatment for moderate acne vulgaris were enrolled into the study. The subjects were randomly assigned study medication from either the treatment or placebo groups. Each group was treated for 6 treatment cycles.

Primary efficacy variables

The primary efficacy variables were the percentage change from baseline to endpoint (ie, cycle 6 data with missing values replaced in accordance with the last observation carried forward [LOCF] procedure) in inflammatory lesion counts (including papules, pustules, and nodules), non-inflammatory lesion counts (including open and closed comedones) and total lesion counts, as well as the percent of subjects classified as '0' (clear skin) or '1' (almost clear skin) on the 6-point Investigator Static Global Assessment (ISGA) scale.

No relevant differences were found when the individual study results were compared with the pooled data of studies A25083 and A25152. Therefore, the pooled data were considered representative of the overall study population. The data presented below is based on the integrated analysis.

Based on the pooled data of studies A25083 and A25152, a total of 893 women were assigned to the amended FAS of the efficacy assessment, ie, 451 women in the YAZ group and 442 in the placebo group). Results of all 4 primary efficacy variables (inflammatory lesion, non-inflammatory lesion, total lesion counts, and subjects with a 'clear' or 'almost clear' rating on the ISGA scale) clearly demonstrated that YAZ was statistically significantly more effective than placebo in the treatment of moderate acne vulgaris. The same applied to the secondary variables (papules, pustules, closed and open comedones) which improved substantially during treatment with YAZ.

7.1.2.3.1 Further confirmatory data in literature

A literature review of the Biomedical Core Database⁷ was conducted in July 2011 for COC therapy of acne vulgaris. For the combination of DRSP 3 mg and EE 0.02 mg (YAZ), the publications that exist are related to the efficacy trials supporting its approval for moderate acne—already cited in this document—or review articles. YAZ is one of three OC preparations in the US with an FDA-approved indication for the treatment of acne; the others are Ortho Tri-Cyclen and Estrostep Fe.

There were four studies identified which evaluated the combination of DRSP 3 mg and EE 0.03 mg (Yasmin) for the treatment of acne, in each case comparing it to another OC preparation. In three of the studies the comparator OCs contained antiandrogenic progestins not available in the US: chlormadinone acetate (CMA)(Lello et al., 2008; Sabatini et al., 2007) and cyproterone acetate (CPA)(van Vloten et al., 2002). The final study involved a comparator OC marketed in the US (Ortho Tri-Cyclen®), also approved for acne, with the progestin NGM (Thornycroft et al., 2004)—antiandrogenic as well but not as potent as the first two mentioned. In all instances the DRSP preparation was found to be effective. In one of the comparisons to CMA, the DRSP preparation was found to be inferior (Sabatini et al., 2007) while in the other it was found to be superior (Lello et al., 2008). In the comparison to CPA (van Vloten et al., 2002) it was found to be equal and when compared to NGM (Thornycroft et al., 2004) it was found to be superior.

7.1.3 Postmarketing efficacy studies

7.1.3.1 INAS efficacy data

Outcome data from 52,218 US participants in the INAS study—a large, prospective, controlled, noninterventional, long-term cohort study with active surveillance of the study participants, were used to estimate real-life effectiveness of OC pills by progestogen, length of pill-free interval, and BMI while focusing on the effect of progestogens with a

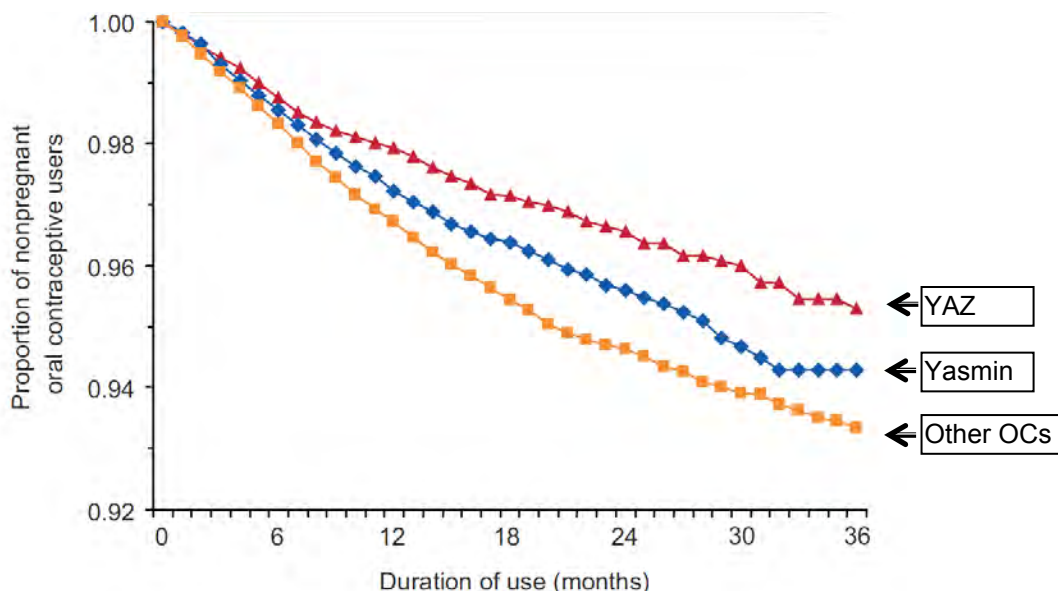
⁷ . This resource encompasses 6 databases with one search strategy: Medline, Embase, Biosis, Current Contents, Derwent Drug file, Product Literature Information

long half-life and on 24-day OC pill regimens. Patients who were prescribed OCs after discussion with their health care providers were eligible for recruitment, and as such could potentially utilize any OC preparation available in the U.S. at the time; the study began in 2005 and is ongoing—with the US recruitment phase having completed in 2008.

Based on 1,634 unintended pregnancies during 73,269 woman-years of OC pill exposure, life-table estimates of contraceptive failure for a 24-day regimen of DRSP and EE and 21-day regimens of other progestogens were 2.1% and 3.5% after the first study year, and 4.7% and 6.7% after the third year ([Figure 7-1](#)). The adjusted hazard ratio was 0.7 (95% confidence interval 0.6–0.8). Direct comparisons of the respective 24-day and 21-day regimens of DRSP and norethisterone, showed lower contraceptive failure rates for 24-day regimens ([Figure 7-2](#)).

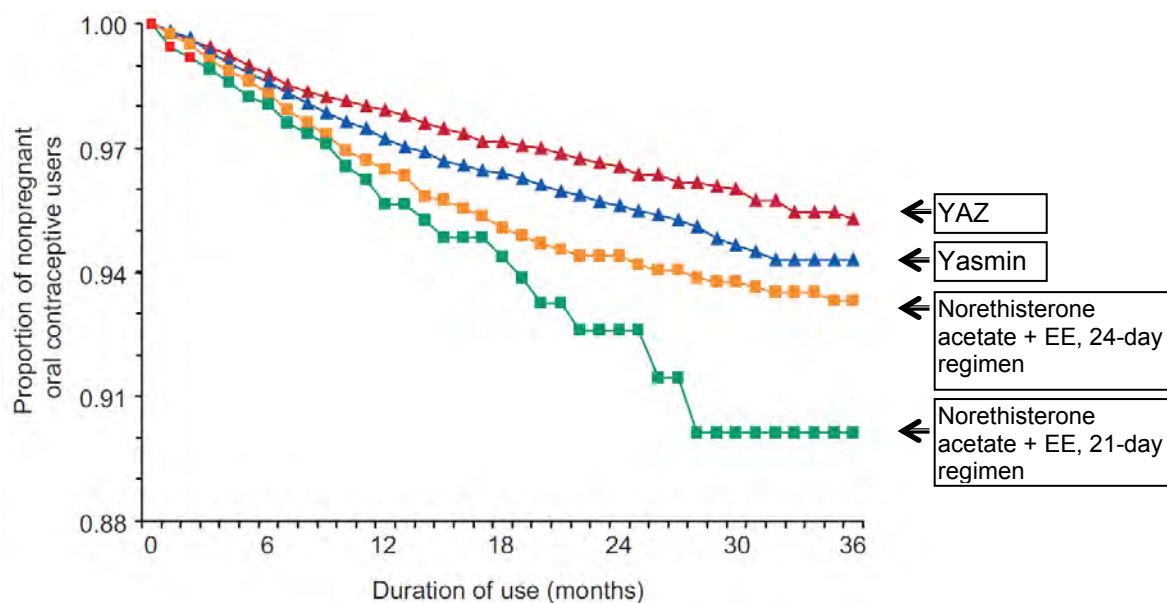
The 24-day OC regimen containing a progestogen with a long half-life showed higher contraceptive effectiveness under routine medical conditions compared with conventional 21-day regimens, including its own counterpart, with respect to steroid combinations. Of the 24-day OC regimens evaluated in the study, the combination of DRSP and EE demonstrated the highest effectiveness. Because of the observational nature of the study, it is possible that results were influenced by residual confounding or bias, which can never be entirely eliminated in such a design and thus represents a limitation to the conclusions. It is nonetheless plausible that a 24-day regimen of DRSP or any other progestin with a long half-life yields better effectiveness than a 21-day regimen of DRSP or a 24-day regimen of a progestogen with a shorter half-life under conditions of imperfect or typical use. The results support that the pharmacokinetic properties of the progestogen and the shorter pill-free interval contribute to the observed differences between DRSP and EE in a 24-day vs. conventional 21-day regimens of other progestogens. A pharmacodynamic study comparing ovarian suppression of DRSP and EE in both 21- and 24-day regimens demonstrated greater ovarian suppression as assessed by Hoogland scores with the 24-day regimen and lends additional support to the plausibility of the differences observed in the INAS study ([Klipping et al., 2008](#)).

Figure 7-1: Life-Table Estimates of Contraceptive Failure Associated With the Use of 24-Day Regimens of DRSP and EE, 21-Day Regimens of DRSP and EE, and Other Oral Contraceptive Pills



Reference: Dinger. Real-life oral contraceptive pill effectiveness. *Obstet Gynecol* 2011;117:33-40, Figure 3.

Figure 7-2: Life-Table Estimates of Contraceptive Failure. Comparison of Two 24-Day and Two 21-Day Regimens of DRSP and EE (triangle) and Norethisterone Acetate an EE (square)



Reference: Dinger. Real-life oral contraceptive pill effectiveness. *Obstet Gynecol* 2011;117:33-40, Figure 4.

7.1.4 Safety in clinical trials

A total of 14 clinical studies provide information on the tolerability and safety of YAZ and YAZ combined with Metafolin (approved in the US with the tradename Beyaz). Among them are 9 studies to evaluate the safety of DRSP 3 mg /EE 0.02 mg as an OC based on a 24-day (YAZ) or 21-day (Yasminelle) regimen, 4 studies to investigate the use of YAZ in the treatment of acne (2 studies) or PMDD (2 studies), and 1 study to investigate the use of Beyaz for increasing folate levels.

The assessment of safety generally corresponds to the full analysis set (FAS) defined as the dataset comprising all women who took study medication at least once and for whom at least 1 post-baseline observation was available. Exceptions to this definition were the acne studies (A25093 and A25152) for which data from all women randomized to treatment and dispensed study medication were evaluated.

An overview of these studies is provided below in [Table 7-4](#).

Table 7-4: Overview of Clinical Studies to Assess the Tolerability and Safety of YAZ and Beyaz

Study no. (protocol no.)	Phase	Short title	Treatment	Duration	No. of women (FAS)	
OC studies						
A12007 (303740)	3	Pearl Index	YAZ	13 cycles	YAZ:	1,027
A30713 (308021)	3	Pearl Index	YAZ	13 cycles	YAZ:	1,101
A29551 (308020)	3	Bleeding pattern and cycle control	YAZ versus Mercilon	7 cycles	YAZ:	229
					Mercilon:	220
A09151 (301888)	3	Lipid, hemostatic and carbohydrate profile	YAZ versus Mercilon	7 cycles	YAZ:	29
					Mercilon:	30
A25848 (308382)	2	Ovulation inhibition	YAZ versus Yasminelle	3 cycles	YAZ:	52
					Yasminelle:	52
A15129 (303860)	3	Pearl Index	Yasminelle	26 cycles	Yasminelle:	516
A09653 (14523)	3	Bleeding pattern and cycle control	Yasminelle versus Mercilon	7 cycles	Yasminelle:	220
					Mercilon:	221
A09372 (14588 ME97133)	2	Ovulation inhibition in Caucasian women	Yasminelle	2 cycles	Yasminelle:	30
A11401 (305466)	2	Ovulation inhibition in Japanese women	Yasminelle	2 cycles	Yasminelle:	23
PMDD studies						
A21566 (304049)	3	PMDD	YAZ versus placebo	3 cycles	YAZ:	231
					Placebo:	218
A07545 (305141)	3	PMDD	YAZ versus placebo (crossover)	3 cycles per treatment	YAZ:	55 ^a
					Placebo:	49
Acne studies						
A25083 (306820)	3	Moderate acne vulgaris	YAZ versus placebo	6 cycles	YAZ:	266
					Placebo:	268
A25152 (306996)	3	Moderate acne vulgaris	YAZ versus placebo	6 cycles	YAZ:	270
					Placebo:	268
Folate study						
A43598 (310662)	3	Folate status	YAZ+ Metafolin versus YAZ	6 cycles	YAZ + Metafolin:	285
					YAZ:	94

^a due to the crossover design, several women are included in both treatment groups

7.1.4.1 Results – oral contraception

7.1.4.1.1 Study population for the safety assessment

Exposure

Based on the clinical studies to investigate the tolerability and safety of YAZ or Yasminelle as OCs (referred to as ‘OC studies’), a total of 3,750 women were included in the overall safety assessment, among them 2,438 women treated with YAZ, 841 women with Yasminelle, and 471 women with Mercilon®.

7.1.4.1.2 Medically relevant adverse events with respect to oral contraceptives

In the course of the clinical development program of YAZ, particular attention was paid to AEs considered to be medically relevant to hormonal contraceptive use, including VTEs.

In accordance with the CPMP Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Diseases (CPMP/EWP/563/98), DVT and PE were considered to be cases of VTEs, but cases of superficial thrombophlebitis were not included. No confirmed VTEs were reported for women treated with YAZ in the OC studies. Although 1 woman on YAZ in study A30713 was initially diagnosed with thrombosis, this was not confirmed by diagnostic means, and she was given the final diagnosis of enthesopathy of the left extremity, a disease of muscular insertions and tendons.

For purposes of further safety assessment, the data accumulated for Yasminelle (DRSP 3 mg/EE 0.02 mg in a 21-day regimen, not approved in the US) were combined with the data from YAZ in NDA 21-676. This yields a total of 3279 women treated with either YAZ or Yasminelle. Two women treated with Yasminelle had confirmed PE, and another woman on Yasminelle had a suspected thrombosis in the right leg.

In summary, the exposure of women treated with YAZ in the OC clinical studies is too limited to adequately quantify the risk of rare events such as VTE. Nevertheless, the findings observed for YAZ were in line with the safety profile of other COCs.

7.1.4.1.3 Clinical laboratory evaluations

Depending on the different study design and objectives, laboratory variables were assessed at varying time points during the individual studies.

Study A09151 was conducted to assess the impact of YAZ with respect to metabolic parameters in women treated with either YAZ or Mercilon for 7 cycles. The metabolic parameters were investigated as primary or secondary parameters and recorded in detail over time. No significant differences in any of the lipid, hemostasis, or carbohydrate parameters investigated were observed between the 2 treatments. These findings did not

give rise to any safety concerns related to metabolic parameter changes in women treated with YAZ.

7.1.4.2 Results of secondary indications

7.1.4.2.1 PMDD

Two phase 3 studies (A 21566 and A07545) were conducted to investigate the safety of YAZ in the treatment of symptoms related to PMDD. Both studies were multicenter, double-blind, randomized, placebo-controlled studies and conducted in the US. Study A21566 was designed as a parallel group study with a study duration of 3 cycles. Study A07545 was a crossover study in which women were treated for 3 cycles, followed by 1 washout cycle and another 3 treatment cycles.

A total of 553 women were included in the PMDD studies, with 286 women treated with YAZ and 267 women with placebo. An analysis of data from the PMDD studies did not give rise to any safety concerns. No cases of VTE were reported with YAZ treatment.

7.1.4.2.2 Acne vulgaris

Two phase 3 studies (A25083 and A25152) were conducted to investigate the safety of YAZ in the treatment of moderate acne vulgaris. Both studies were multicenter, double-blind, randomized, placebo-controlled studies, identical in design and study course, except for additional hormone measurements performed in a subgroup of women in study A25083.

A total of 1,072 women were assigned to the FAS of the safety assessment of the acne studies, with 536 women included in each of the YAZ and placebo groups. An analysis of data from the acne studies did not give rise to any safety concerns. No cases of VTE were reported with YAZ treatment.

7.1.4.3 Results – Beyaz

In the phase 3 folate study (A43598), a total of 379 women were included, with 94 women exposed to YAZ and 285 women exposed to Beyaz.

No cases of VTE were reported with Beyaz treatment. An analysis of data did not give rise to any safety concerns compared with the side effect profile of other COCs.

7.1.4.4 Safety conclusions

The safety of YAZ/Beyaz is well established. On the basis of the results of the various clinical development programs that comprised 3,279 women from the clinical studies to investigate YAZ/Yasminelle as an OC, 286 women from the studies that investigated YAZ in the treatment of symptoms related to PMDD, 536 women from the studies that investigated YAZ in the treatment of moderate acne vulgaris, and 94 women on YAZ and

285 women on Beyaz to evaluate folate levels, the safety findings were consistent with the side effect profile of other COCs.

7.1.5 Postmarketing safety studies

7.1.5.1 VTE data

Postmarketing studies investigating the risk of VTE with YAZ are presented in [Section 4.8.1](#).

7.1.5.2 Other publications on VTE risk with YAZ

The 2011 BMJ publication by Lidegaard et al includes a small subset of Yasminelle and YAZ users which is discussed in [Section 4.8.1](#).

7.1.6 Benefit-risk profile of YAZ

YAZ is a 24-4 COC regimen with 0.02 mg of EE and 3.0 mg of DRSP. YAZ has undergone a comprehensive development program, relative to its initial US approval for contraception in 2006, which has continued through the additional approvals related to PMDD, moderate acne and the most recent approval of Beyaz (DRSP 3 mg/EE 0.02 mg and levomefolate calcium 0.451 mg) in 2010. The accumulated scientific evidence continues to demonstrate that YAZ is an effective form of contraception. It is one of three COC formulations currently approved, in women seeking contraception, for the treatment of moderate acne. It is also differentiated from other COCs by offering, in women seeking contraception, treatment for PMDD.

With respect to the unique antimineralocorticoid properties of DRSP, the YAZ and Yasmin labels provide the same guidance, and no increased incidence of AEs related to this aspect of the labeling have been identified. When used in accordance with the product labeling, the risk profile for YAZ is aligned with the class label for COCs.

With respect to the risk of VTE, the current class label for all approved COC formulations (PLR format) reflects a risk in the range of 3-9 per 10,000 WY for COC users, with the risk being highest during the first year of use. As to the comparative risk of VTE between YAZ and other COC formulations, all interim results from the prospective INAS-OC study, a post-approval commitment to the FDA and the EMA that is currently ongoing, indicate that the risk of VTE in YAZ users is comparable to that seen with the other COCs studied, including LNG-containing COCs.

In summary, YAZ is a differentiated COC through its formulation (0.02 mg EE), its dosing regimen (24/4), and its indications. The overall benefit-risk profile of YAZ (and Beyaz) is favorable and aligns with the general class of COCs, including LNG-containing COCs, when used in accordance with the product labeling.

8. Conclusions

Yasmin and YAZ are among the most extensively studied COCs, both in their respective clinical development programs as well as studies conducted since their approval, including the postmarketing commitment safety studies.

Both Yasmin and YAZ are clinically differentiated from other COCs, with DRSP as the progestin component. The differentiation associated with DRSP includes the long half life (30 hours) of DRSP, and its antimineralocorticoid and antiandrogenic activity. Both Yasmin and YAZ are effective COCs, as confirmed through their clinical development programs, as well as the recently reported results from the INAS study.

Both Yasmin and YAZ have expanded the range of contraceptive options available to women and their health care providers. In the case of YAZ, it is further differentiated through its dosing regimen, with 24 days of active therapy and 4 days of placebo, the secondary indication for moderate acne as well as its secondary indication of PMDD. YAZ is the only approved alternative to selective serotonin reuptake inhibitors (SSRIs) for PMDD. Safyral and Beyaz include the additional secondary indication of raising serum folate levels and are the only FDA-approved COCs with this indication.

Against this background, there remains the issue of the risk of VTE associated with the use of Yasmin or YAZ, relative to other COCs. The inherent differences between Yasmin and YAZ require looking at the issue separately for each COC.

The discordant findings around the risk of VTE apply only to Yasmin. As outlined in the current Briefing Document, efforts to accurately assess the comparative risk of VTE associated with different COCs demands studies that implement rigorous quality standards and appropriately account for key factors specific for the complex medical issue of VTE risk with COCs. When looking across the current studies of interest, the Ingenix, EURAS, LASS, and German Case-Control study, all of which combined rigorous standards, particularly for observational studies, as well appropriately accounting for these key factors align in their findings. In aggregate, these studies provide strong evidence that the risk of VTE with Yasmin is similar to the other COCs studied, including LNG-containing COCs. By contrast, the Danish (and Lidegaard reanalysis), MEGA, US PharMetrics, UK GPRD studies, and FDA-funded study, have important design limitations, which may limit their ability to appropriately control for key factors involved in the assessment of the VTE risk with COCs. The important design limitations of these latter five studies produce unreliable results. Many of the findings from each of these five studies fail to align with the well-established body of scientific literature on the risk of VTE with COCs, some of which were generated in the past by the same investigators. In addition, the estimate for the risk of VTE with LNG-containing COCs shows great variability across these five studies and the prior work from many of the same investigators. In the end, clinical practice should be guided by the best available evidence. The best evidence is derived from the better designed and conducted studies, and the conclusion is that the risk of VTE with Yasmin is similar to the risk seen with the other COCs studied, including LNG-containing COCs.

In terms of YAZ, the ongoing INAS study combines rigorous standards for observational studies as well appropriately accounting for the key factors relative to the risk of VTE with COCs. The interim data for YAZ already encompass the entire cohort of US women enrolled in the study. The data, already shared with the FDA through the regular submission of interim reports, provide good evidence that the risk of VTE with YAZ is similar to the other COCs studied, including LNG-containing COCs. In the absence of any data to the contrary, and the evidence already accumulated the risk of VTE with YAZ is similar to the risk seen with the other COCs studied, including LNG-containing COCs.

The sponsor's position remains that Yasmin, Safyral, YAZ, and Beyaz have a favorable benefit-risk profile when used in accordance with approved labeling.

9. Reference list

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10. Appendices

10.1 Appendix 1: Sponsor's Clinical Expert Statement on 2009 BMJ Publications (Danish Registry study [Lidegaard et al. 2009] and MEGA study [van Hylckama Vlieg et al. 2009])

The following text was initially submitted to the FDA in October 2009 as part of the response to the 2009 BMJ publications

Clinical Expert Statement

Newly published studies on the risk of VTE during use of low ethinylestradiol dose oral contraceptives, including Yasmin

Author: Dr. Maureen Cronin and Dr. Leo Plouffe, Jr Date: 16 October 2009

Table of contents

1. Introduction	3
2. Recent publications on low dose OC Cardiovascular Safety	4
2.1 Lidegaard Ø et al. ¹	4
2.2 Van Vlieg A et al. ²	6
3. Bayer Schering Pharma Post Authorization Safety Studies for Yasmin.....	9
3.1 Completed BSP PASS studies for Yasmin.....	10
3.1.1 European Active Surveillance (EURAS) OC Study	10
3.1.2 Ingenix Yasmin Study.....	12
3.2 Ongoing BSP PASS Studies involving Yasmin.....	14
3.2.1 Interim Results of the LASS Study	14
3.2.2 Interim Results of the INAS study	17
4. Overall Bayer Schering Pharma's Conclusions	18
References.....	20
List of abbreviations	21
CV of Medical Expert – Dr. Cronin	23
CV of Medical Expert – Dr. Plouffe, Jr.....	24

1. Introduction

The purpose of this Expert Statement is to summarize the current safety data for Yasmin (drospirenone 3mg / ethinyl estradiol 0.03mg – 21 days) in light of two recently published studies^{1,2} on the risk of venous thrombosis (VTE) associated with OC use and put these in context given the already existing body of scientific evidence.

These two retrospective studies^{1,2} were published in the British Medical Journal (BMJ) on August 14, 2009. Both studies^{1,2} assessed the risk of venous thrombosis (VTE) in users of different types of hormonal contraception. The risks were assessed for the use of oral contraceptives (OCs) containing different progestins. The study results suggest that OCs have a differential VTE risk based on the progestin component, including drospirenone^{1,2}.

The results of these two studies^{1,2} are not consistent with the large amount of data already generated in clinical and post-marketing trials. As part of its post-marketing commitments to EMEA and the FDA for its oral contraceptives, Bayer Schering Pharma sponsored two large observational studies (EURAS OC³ and Ingenix Yasmin⁴) in Europe and the United States. Both of these prospective studies^{3,4} were sufficiently powered to assess differences in the risk of VTE between preparations containing different progestins and were designed to achieve balance between the cohorts, e.g., by controlling for confounding factors. Both the EURAS³ and Ingenix⁴ studies were conducted diligently, have been completed, have been reported to the EMEA and US FDA, and have been presented to the general scientific community. Together, EURAS³ and Ingenix⁴ encompass more than 120,000 oral contraceptive users, respectively in Europe and in the United States, and have independently demonstrated that users taking low-dose oral contraceptives have similar venous thrombotic risk regardless of the progestin used, including drospirenone.

The efficacy and safety of Yasmin has been extensively characterized during clinical development and has been confirmed in clinical practice and large prospective postmarketing studies^{3,4} after marketing authorization was obtained. The estimated overall cumulative patient exposure by the end of July 2009 was a total of 468,239,783 cycles (36,018,445 women-years). All relevant safety data have been presented and discussed in the Periodic Safety Update Reports (PSURs). The next PSUR (Number 12) will be submitted in November 2009.

In addition to the current internal scientific analysis, Bayer Schering has retained two external independent expert consultants to provide their insights into the Lidegaard et al¹ and the van Hylckama Vlieg et al² studies. Their Expert Reports are attached. (Prof. Samy Suissa, Dr. Samuel Shapiro)

2. Recent publications on low dose OC Cardiovascular Safety

2.1 Lidegaard Ø et al.¹

Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009; 339: b2890

Results:

Data on all VTEs occurring in hospitalized Danish women between the age of 15 to 49 from January 1995 through December 2005 were gathered in a national database for hospital discharge diagnoses. Women with previous cardiovascular events or malignant disease were excluded. Time periods for an ongoing pregnancy were excluded from the person-time analysis. The data were linked with data on redeemed hormonal contraception prescriptions. The linked data were analyzed in a database cohort study design. Confounding factors for which the analysis was adjusted for were age, calendar year, and level of education.

10.4 million women years (WY) were recorded, 3.3 million WY in receipt of oral contraceptives. In total, 4213 VTEs were observed, 2045 in current users of oral contraceptives. The overall absolute risk of VTE per 10 000 WY in non-users of oral contraceptives was 3.01 and in current users was 6.29. Compared with non-users of COCs the rate ratio (RR) of VTE in current users decreased beyond the first year of use (<1 year 4.17, 95% confidence interval 3.73 to 4.66, 1-4 years 2.98, 2.73 to 3.26, and >4 years 2.76, 2.53 to 3.02; P<0.001) and with decreasing dose of estrogen. Compared with oral contraceptives containing levonorgestrel (LNG) and with the same dose of estrogen (30-40 µg) and length of use, the RR for oral contraceptives with norethisterone was 0.98 (0.71 to 1.37), with norgestimate 1.19 (0.96 to 1.47), with desogestrel 1.82 (1.49 to 2.22), with gestodene 1.86 (1.59 to 2.18), with drospirenone (DRSP) 1.64 (1.27 to 2.10), and with cyproterone 1.88 (1.47 to 2.42). For the rate ratio calculation also the length of use was adjusted for.

Bayer Schering Pharma's Assessment:

Several findings from this study are concordant with the some well established data about the VTE risk associated with OC use. For example, a lower risk of VTE with lower EE doses compared to preparations with higher doses (e.g. 0.05mg versus 0.03-0.04mg EE). However, the fact that some analyses from this study align with those from previously published studies does not de facto validate the methodology used in this study. Indeed, there are many shortcomings that compromise the reliability of several of the additional analyses and conclusions proposed by the authors.

The most unexpected finding in the study is the lack of higher risk of VTE during the first year of use (<1 year) use of levonorgestrel containing OCs (table 2). This contrasts with the expected finding that the highest risk for VTE is found during the first year of use, and applies to all of the other progestins included in this study. This finding, a higher risk during the early phase of treatment, has been a consistent finding for all progestins, including levonorgestrel, in most studies that have looked into this issue, including the EURAS OC study³ as well as the study published simultaneously in BMJ (MEGA study² - van Vlieg A et al – see below). The most likely explanation for this unexpected and discordant finding from the Lidegaard et al study relates to the fact that data on levonorgestrel containing OC use before the study start in 1995 was not available. It was therefore not possible for the study investigators to accurately

categorize duration of use according to the categories designated by the authors themselves (<1, 1-4 years and >4 years). This issue, often referred to as ‘left censoring’ of the prescription data, is highly likely to have led to a misclassification of long-term levonorgestrel users as short term users. By contrast, drospirenone was first available in Denmark only in 2001 and thus all drospirenone users who started on drospirenone were identified as such. The overall consequence of this misclassification of patients on levonorgestrel for duration of use resulted in a marked underestimate of the rate of VTE for subjects in the “first year user” group of levonorgestrel. Given that significantly more VTE events occur during the first year of use of any OC, this uncorrected bias in favor of levonorgestrel invalidates any further comparison to the risk of VTE for other progestins. In short, in the comparison of drospirenone with levonorgestrel, the underestimation of the risk for short-term use of levonorgestrel in the Lidegaard et al study could easily have resulted in the authors’ overestimation of the RR, reported as 1.64 (95% CI: 1.27-2.10). As stated by Shapiro, “The differential misclassification of duration of use is important, as OCs increase VTE risk maximally during the first months of use, after which the risk declines. Therefore long-term users have a substantially lower risk of VTE than do short-term users.” (see accompanying Expert Report from Dr. Samuel Shapiro)

The bias in favor of levonorgestrel is further supported by close scrutiny of the data. For example, the incidence rate for VTE in the DRSP cohort (7.8/10,000 WY) is aligned with other data sets, most likely reflecting the inclusion of the vast majority of applicable subjects from the onset of use, given that Yasmin was marketed in the seventh year of the study. By contrast, the incidence rate for LNG (5.5/10,000 WY) is lower than expected from other existing data^{2,3,4} and further confirm the strong likelihood that the LNG data are favorably influenced by the ascertainment bias (left censorship of the data described above).

Additional methodological aspects of this study call for caution in interpreting the results. The retrospective nature of the study is clearly acknowledged but is nonetheless a limitation that should portray this study as “hypothesis generating” at most. Several specific points in the methods are not clearly outlined in the publication. Further clarification from the authors, and likely a direct exploration from the primary database would be essential to resolve these issues. In the absence of these steps, these areas of uncertainty must be viewed as shortcomings and are important in considering how one should perceive the study relative to the already existing and published data.

For example, the study investigators were also not able to assess differences in known risk factors for VTE, such as obesity as measured by Body Mass Index (BMI) and family history of VTE, in the users of the different types of OCs, classified by progestin component. The missing data for these major confounders, is problematic especially for the comparison between the drospirenone containing OC and the chosen reference progestin, levonorgestrel. Drospirenone containing OCs were found to be preferentially prescribed to obese OC users.³ The EURAS OC study, which was conducted in seven European countries (including 167 actively participating centers in Denmark) demonstrated that the percentage of obese (BMI ≥ 30.0) women was higher in the drospirenone-containing OC cohort compared to the Other OCs cohort and the levonorgestrel-containing OC cohort (rate ratios 1.8 and 1.6 respectively).

Also women with a family history for VTE often receive the most recently marketed OC in the ‘mistaken belief’ that they are safer (see accompanying Expert Report from Dr. Samuel Shapiro). The EURAS study also demonstrated that Yasmin users had a 1.2-fold higher risk for a positive family history compared to users of other OCs.³ In addition to the ‘left censorship’ issue,

Lidegaard et al appear to calculate the duration of use as the aggregate use over time, regardless of whether or not the use was continuous or in intervals; differences in the pattern of use among different preparations could further influence the results.

Conclusion:

For the study period selected, 'left censorship' of prescription data appear to have led to an underestimation of the incidence rate in short term users (<1 yr) of levonorgestrel, which invalidates the comparison to drospirenone. Therefore, the comparison of the VTE risk between drospirenone and levonorgestrel containing OCs is not valid and thus the study results indicating a difference in VTE risk for drospirenone containing OCs compared to levonorgestrel containing OCs has to be questioned. Additional ambiguities around the methodology of the study, such as lack of adequate control for relevant confounding factors, seriously limit the overall contribution of this paper to the already existing literature in the field.

2.2 Van Vlieg A et al. ²

The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009; 339: b2921

Methods:

This case-control study analyzed data derived from the MEGA (Multiple Environmental and Genetic Assessments of risk factors for venous thrombosis study) study database, a large, population based, case-control study on risk factors for venous thrombosis conducted in six anticoagulation clinics in the Netherlands.

Data on all first episodes of VTEs occurring in patients < 70 years from March 1999 through September 2004 were included in the MEGA study database. For this analysis, only women aged 18 -50 years were included. Women who were post-menopausal, pregnant or within 4 weeks postpartum, or using other forms of hormonal contraception (not oral contraceptives) were excluded. Women with cancer were not excluded.

The controls were gathered from two different sources: either from the female partners of the men in the MEGA study that had experienced a VTE (40.5%) or from random digit dialing (59.5%). The groups were pooled and adjusted by inclusion date.

All of the participants filled in a standardized questionnaire on risk factors for venous thrombosis such as family history of thrombosis, pregnancy, and oral contraceptive use in the year before the index date. The index date was the date of the thrombotic event for patients and their partners and the date of filling in the questionnaire for the random controls. The questionnaire was sent to all patients and their partners within a few weeks after the index date. For the random controls, the questionnaire was sent after their agreement to participate.

Relative risks were assessed by calculating odds ratios and 95% confidence intervals. Risk estimates were adjusted by unconditional logistic regression, and confidence intervals were derived from the model. The odds ratios in the overall analysis of the risk associated with current oral contraceptive use were adjusted for age. When analyzing the thrombotic risk associated with

dose of oestrogen or type of progestogen, an additional adjustment was made for date of inclusion (divided in a total of 12 periods of 6 calendar months spanning 1999-2004).

For current oral contraceptive use, the risk of venous thrombosis was calculated for all users of oral contraceptives, and separately for the different types of oral contraceptives, compared with non-users (never users and past users combined). Because a positive family history of venous thrombosis has been hypothesised to lead to preferential prescription of specific types of oral contraceptive, a positive family history was taken into account. A positive family history was defined as a participant having at least one parent or sibling with a history of venous thrombosis as reported by the participants. Body mass index (weight (kg)/(height (m)²)), also a potential confounder in the association between different types of oral contraceptives and the risk of venous thrombosis, was calculated using weight and height as stated by the participants in the questionnaire.

Odds ratios calculated by cross tabulation with a 95% confidence interval according to Woolf's method; adjusted odds ratios estimated by unconditional logistic regression, standard errors derived from the model.

Results:

Currently available oral contraceptives increased the risk of venous thrombosis fivefold compared with non-use (odds ratio 5.0, 95% CI 4.2 to 5.8). The risk differed by type of progestogen and dose of oestrogen. The use of oral contraceptives containing levonorgestrel was associated with an almost fourfold increased risk of venous thrombosis (odds ratio 3.6, 2.9 to 4.6) relative to non-users, whereas the risk of venous thrombosis compared with non-use was increased 5.6-fold for gestodene (5.6, 3.7 to 8.4), 7.3-fold for desogestrel (7.3, 5.3 to 10.0), 6.8-fold for cyproterone acetate (6.8, 4.7 to 10.0), and 6.3-fold for drospirenone (6.3, 2.9 to 13.7). The risk of venous thrombosis was positively associated with oestrogen dose. A high risk of venous thrombosis was confirmed during the first months of oral contraceptive use irrespective of the type of oral contraceptives.

Bayer Schering Pharma's Assessment:

The van Hylckama Vlieg et al², similar to the Lidegaard¹ study, reaches many conclusions that align with the existing literature. For example, the study confirms an overall increased risk for VTE in all OC users regardless of preparation used as well as a reduction of risk with a reduction of the ethinyl estradiol dose.

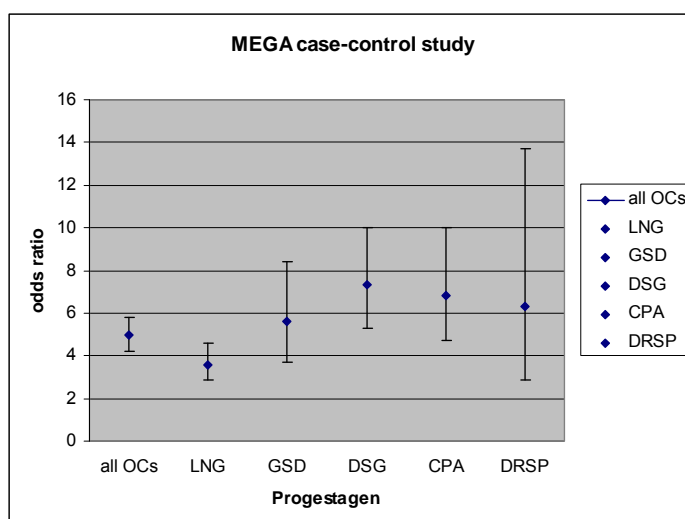
Several elements of the methodological approach used by these authors bring into question the robustness of the data generated, as we outline below and as is highlighted in the Expert Reports by Dr. Shapiro and Prof Suissa. Ultimately, a key challenge is to reconcile the fact that the comparative analyses between the various progestins and levonorgestrel for the most part fail to achieve statistical significance, yet the authors conclude definitively that there is a difference between preparations. For drospirenone compared to levonorgestrel, the authors report an odds ratio of 1.7 (95% CI: 0.7-3.9). It should be highlighted that of the 1524 patients in the thrombosis group, 485 were in the levonorgestrel cohort and 19 in the drospirenone. Given these small numbers as the basis of the comparison, and the fact that the result is not statistically significant, it is difficult to understand why the authors would further engage in comparing the risk estimate during short term use (ie; < 3months). Again, their conclusion that there is a

difference between the risk for levonorgestrel and drospirenone is not supported by their data (odds ratio 1.9 - 95% CI: 0.2-21.3). Given the few cases on drospirenone as the basis for the comparison and the non-statistically significant difference, their data do not support their stated conclusions. At best, these retrospective data would support further exploration, in the absence of data from methodologically superior studies.

The lack of statistical significance is equally evident in comparisons of the VTE risk between the progestins compared to no use, where the 95% confidence intervals are – in most cases – overlapping. Therefore these comparisons are not statistically significant and thus do not support the unqualified statement that there is a difference in risk between OC containing drospirenone and levonorgestrel.

Please see the following graph for a presentation of the OR (with 95% CIs) for the various progestins compared to no OC use.

Dutch MEGA case-control study



From a methodological perspective, while the potential confounders of age, date of inclusion, family history, BMI, and smoking are mentioned, it is not clear if these were included in the logistic regression for the comparison of the progestins. They are not mentioned in the explaining footnote. The investigators state they adjusted for age and inclusion categories; however the effect of these adjustments is not clear. For example, the crude OR for the comparison between DRSP vs LNG is 1.04 (95% CI: 0.49 to 2.28) (see Expert Report by Dr. Shapiro) but changes to 1.7 (95% CI: 0.7 to 3.9) after adjustment.

Additionally, the approach to establishing a control group appears highly unorthodox. It is composed of a mix of female partners of males with a history of VTE and who enrolled in the MEGA study as well as women recruited from the overall general population of the Netherlands, identified by random-digit dialling. A more customary approach would have relied entirely on

this latter method.⁵ Controls should represent those in the population at risk of becoming a case, and partners of the male cases in the MEGA data are not likely to be representative of the female Dutch population at risk of VTE.

Conclusion:

The most highlighted results - the putative differential risk for the various progestins - are not statistically significantly different (wide overlapping of the 95% CI) and thus do not suggest real differences in risk for the different preparations.

The apparent lack of adjustment for these comparisons for the most important confounding factors such as coagulation mutations and BMI - although the data were readily available – a serious shortcoming.

The selection of the controls was not optimal and unlikely representative of the general population.

Therefore the study results for the comparison of drospirenone with levonorgestrel were not valid and thus, in opposition to the claim made by the study investigators, do not demonstrate an increased VTE risk for drospirenone containing OCs compared to levonorgestrel containing OCs.

3. Bayer Schering Pharma Post Authorization Safety Studies for Yasmin

The field of oral contraception has been hampered by an ongoing controversy since the mid 1990's around the potential for a greater risk of VTE with certain progestins over others. The original issue was comparing so-called “second” and “third” generation progestins. The inherent methodological aspects of most of these studies (retrospective, control for risk factors, control for duration of use, prescription bias, recall bias) have fueled a constant debate in the scientific community around the validity and clinical relevance of these findings. The issue is more than of academic interest. A number of clinicians reported that in the wake of the original publications in the mid-1990's, many women abruptly discontinued on their own the use of their oral contraceptive, out of fear and confusion, with an accompanying increase in the overall rate of unintended pregnancies.

With the introduction of a contraceptive with a novel progestin (Yasmin – drospirenone 3.0mg / ethinyl estradiol 0.03mg x 21 days), Bayer Schering (at the time Schering Pharma) was very receptive to the independent requests by the EMEA and the US FDA to conduct robust prospective studies to assess key aspects of the risk profile of drospirenone compared to other progestins. Each regulatory agency provided input into the respective protocols and final approval, the EMEA for the European Active Surveillance Study (EURAS³), and the US FDA for the Ingenix⁴ study. To ensure full independence in the conduct of the study, Bayer Schering provided funding to two independent third parties, who enjoy wide acceptance and recognition as centers of excellence in the field. For EURAS, this was the ZEG (Center for Epidemiology and Health Research, Berlin, Germany). For the USA, this was the Ingenix (i3 Drug Safety, Ingenix, Waltham, Massachusetts, USA) group. Both studies were conducted diligently and have generated regular reports that have been shared with regulatory authorities around the world, as part of the regular reporting process. A number of publications in the scientific literature have also resulted from both studies.

The successful completion of the EURAS³ study, including a high rate of retention of study subjects, has enabled continued study of the population into a study extension, the Long-Term Active Surveillance Study (LASS). The methodology and effective implementation of the EURAS study also prompted setting up a similar study, the International Active Surveillance Study (INAS), with the introduction of a new drospirenone-containing regimen (YAZ – drospirenone 3.0mg and ethinyl estradiol 0.02mg x 24 days). Importantly, INAS received input and final support of both the EMEA and FDA. The study is also being conducted independently (ZEG), is ongoing and is being monitored by an independent Data Safety Monitoring Board (DSMB). To date, the study continues as planned, with the support of the DSMB. Again, regular updates are provided to regulatory authorities through the regulatory reporting process.

So far, the EURAS³ and Ingenix⁴ studies have reported publicly on approximately 125,000 women (of which 38,900 were Yasmin users) that contributed 185,000 WY of observation in the studies. Neither study showed a statistically significant difference in the VTE incidences for combined OCs containing ethinyl estradiol and drospirenone in comparison to other commonly used progestins, including levonorgestrel.

We present below a summary of the data of the EURAS³, Ingenix⁴ and related studies.

3.1 Completed BSP PASS studies for Yasmin

Two post-marketing safety studies were completed in Europe and the US since the last Yasmin's approval. Both were PASS studies. The EURAS OC study³ was a phase 4 commitment to EMEA¹ and the Ingenix Yasmin study⁴ was a phase 4 commitment to the FDA². The major conclusions are reported here in brief.

3.1.1 European Active Surveillance (EURAS) OC Study

Objectives: This prospective, controlled, non-interventional, active surveillance, new users cohort study was designed to characterize the risk of use of oral contraceptives (OCs). The primary outcome of interest was cardiovascular events, in particular the incidence of venous thromboembolic events (VTE) but also arterial thromboembolic events (ATE) and arrhythmia during OC use with particular focus on Yasmin.

Methods: The study was initiated in November 2000, the last patient was enrolled in June 2004, and outcome follow-up was completed in December 2005. 59,510 OC users were enrolled in 7 European countries. After exclusion of protocol violators, 58,647 study participants were followed up for 142,475 women-years of observation. Overall, 1,401 women, or 2.39%, were lost to follow-up. Three user cohorts were followed throughout the study, a DRSP containing OC, an LNG containing OC and Other OC cohort.

¹ Final report submitted to YASMIN[®] NDA 21-098 on June 7, 2006.

² Final report submitted to YASMIN[®] NDA 21-098 on July 7, 2006.

Results: The overall rates of any adverse events (AE) (~1,300 AEs/10⁴WY) and the overall SAE rates were very similar for all 3 OC cohorts (~340 SAEs/10⁴WY). For the main outcomes of interest, cardiovascular events, which include reports on VTE, ATE and arrhythmia, major differences in the risk estimates between cohorts were not found.

In total, 118 VTEs (mainly deep vein thrombosis and pulmonary embolism) were observed in the study:

- DRSP cohort: 26 events (9.1 events/10⁴ WY; 95% CI: 5.9 – 13.3)
- LNG cohort: 25 events (8.0 events/10⁴ WY; 95% CI: 5.2 – 11.7)
- Other OCs cohort: 52 events (9.9 events/10⁴ WY; 95% CI: 7.4 – 13.0)

In total, 25 ATEs (mainly stroke and myocardial infarction) were observed in the study:

- DRSP cohort: 2 events (0.7 events/10⁴ WY; 95% CI: 0.1 – 2.5)
- LNG cohort: 9 events (2.9 events/10⁴ WY; 95% CI: 1.3 – 5.4)
- Other OCs cohort: 9 events (1.7 events/10⁴ WY; 95% CI: 0.8 – 3.2)

Based on Cox regression analysis, using the pre-defined confounder variables (i.e.; for VTE: age, BMI, duration of use, and VTE history; for ATE: age, BMI, smoking and hypertension; for arrhythmia: age and BMI), no increase in risk was found for Yasmin users compared to LNG and Other OC users or for the combination of both of these cohorts (see table below).

Adjusted hazard ratios (HR) and confidence limits for VTE, ATE, TE, and arrhythmia

	Yasmin vs.					
	LNG		Other OCs		LNG & Other OCs	
	HR	95% CI	HR	95% CI	HR	95% CI
VTE	1.05	0.61 - 1.81	0.77	0.48 - 1.26	0.87	0.55 - 1.37
ATE	0.25	0.05 – 1.17	0.34	0.08 – 1.52	0.30	0.07 – 1.29
TE*	0.85	0.51 – 1.42	0.69	0.44 – 1.12	0.76	0.49 – 1.17
Arrhythmia**	0.52	0.22 – 1.22	0.77	0.34 – 1.76	0.65	0.30 – 1.40

* all thromboembolic events (VTE and ATE combined)

** new conditions that required treatment

Overall, all VTE, ATE and TE hazard ratios (adjusted and crude) that compared the DRSP cohort with other OC cohorts are close to or lower than unity and do not suggest a higher risk for Yasmin users. The narrow confidence intervals suggest that the risk for the 3 cohorts is similar.

Investigator's Conclusions:

No major differences were found between the cohorts in the rates for overall AEs and SAEs. Overall, for all outcomes studied an increased risk for Yasmin users compared to users of other OCs (including LNG-containing OCs) was not identified. The study results were robust enough to show non-inferiority of Yasmin regarding the cardiovascular outcomes of interest. These results suggest that the risk of adverse cardiovascular outcomes for Yasmin users do not differ materially from the risks associated with the use of LNG-containing OCs or Other OCs.

Bayer Schering Pharma's Assessment of the EURAS study results

Bayer Schering Pharma agrees with the assessment of the study investigators: No increased risk of VTE and ATE was noted in users of Yasmin, as compared to users of levonorgestrel-OCs, and users of Other-OCs.

The EURAS study is a sufficiently large (112,659 women-years of exposure in the 3 OC-cohorts) and well conducted (e.g. the very low drop-out rate, 100% validation of outcomes of interest, and blinded adjudication of the final results by study independent medical experts) study that provides robust results on the occurrence of rare serious adverse events like VTE and ATE during typical OC use in European women of childbearing age. In particular, the study design and methodology are well suited to deliver precise results on the rates for overall AEs and SAEs, organ-system specific SAEs, overall mortality and outcome-specific mortality, overall cancer and organ-system specific cancer, renal and hepatic dysfunction, unwanted pregnancy, and congenital malformations during OC use in 'real world' conditions.

Overall the EURAS study confirms that for all outcomes studied an increased risk in Yasmin users compared to users of other OCs (including LNG-containing OCs) was not identified. The study demonstrated non-inferiority of Yasmin regarding the cardiovascular outcomes of interest. These results suggest that the risk of adverse cardiovascular outcomes, especially the risk for VTE, for Yasmin use does not differ materially from the risks associated with the use of LNG-containing OCs or Other OCs.

3.1.2 Ingenix Yasmin Study

Objectives: The US Ingenix study ("Dispensing Practices, Health Outcomes, and Pregnancy Outcomes in Women Taking Yasmin") was conducted to assess if the unique antimineralocorticoid properties of Yasmin were related to an increase in hyperkalemia or related outcomes. In addition, the study evaluated the use of Yasmin among women with contraindications or warnings related to its use to assess compliance of healthcare providers with the recommendation to measure serum potassium in the first Yasmin cycle among women receiving long-term therapy with drugs that predispose to increased serum potassium. The study followed up on breakthrough pregnancies that occur in women who are using Yasmin or Other OCs and reported on congenital malformations. During study conduct venous and arterial thromboembolic events were added as study outcomes, in addition to the initially planned adverse events possibly related to hyperkalemia. The setting for the study was a claims database

built from provider, facility, and pharmacy claims at UnitedHealthcare, a large US based health insurance.

Methods: Using information obtained from the claims histories, Yasmin and Other Oral contraceptive (OC) initiators were identified in each calendar quarter of the first three years of Yasmin marketing in the US (2001-2004). A 2-fold larger group of the OC initiators was matched to the Yasmin group using propensity score analysis with a total of 22,429 Yasmin initiators and 44,858 Other OC initiators. The Yasmin group contributed 14,541 and the Other OC group contributed 28,169 person-years respectively. Claims based outcomes were confirmed via abstraction of relevant medical records. There was no difference in risk for hyperkalemia by oral contraceptive exposure state (rate ratio for Yasmin versus Other OC: 0.5; 95% CI 0.0 – 4.9). The rate ratio for hyperkalemia was not meaningfully different from the rate ratios for any of the individual surrogate measures of that condition (arrhythmia, syncope, electrolyte disturbance and myocardial infarction) or that of a composite hyperkalemia endpoint comprising all surrogate measures together (RR 0.9; 95% CI 0.7 – 1.1). Approx 0.5% Yasmin dispensings were to women whose insurance claims indicated possible contraindications. Potassium monitoring was more frequent among women with new dispensings of Yasmin who also received concurrent therapy with drugs that predispose to hyperkalemia than among similar women with new dispensings of Other OCs (40 vs 35%). A validation study confirmed the balance of the propensity scores matching with respect to selected variables not available in the claims data. There were nine congenital malformations in children of Yasmin exposed mothers and 17 congenital malformations in children of the Other OC exposed mothers.

Results: Among Yasmin initiators there were 19 confirmed ATE/VTE events in 14,541 woman-years of follow-up for an absolute incidence rate of 1.3 events per 1,000 woman-years. In the Other OC cohort there were 40 confirmed VTE/ATE events in 28,169 woman years for an absolute incidence of 1.4 events per 1,000 women-years. The crude rate ratio comparing the Yasmin cohort to the Other OC cohort is 0.9, 95% CI 0.5 – 1.6, consistent with a hypothesis of no difference in ATE/VTE incidence between the cohorts.

Conclusions: There was no difference in risk of any of the study outcomes between the Yasmin and the Other OC initiators. No evidence was found of an increased risk of hyperkalemia among Yasmin initiators compared to Other OC initiators. For congenital malformations, there was no demonstrated specific teratogenic effect of Yasmin or Other OC exposure during the estimated window of conception. The risk of VTE/ATE outcomes was similar in women who initiated Yasmin relative to Other OCS. The advisory board concluded that there is no safety signal based on the review of the final data.

Bayer Schering Pharma's Assessment of the Ingenix Yasmin Study Results

The Ingenix study was a prospective cohort study based on claims data from United Health Care, a major US health care provider. This study was part of a phase 4 commitment for Yasmin and was contracted by Berlex and conducted by Dr. A. Walker (Ingenix). Pharmacy claims were used to identify a cohort of Yasmin and other OC users with follow-up using the International Classification of Diseases (ICD)-9 codes reported for billing purposes. The cohorts were matched through propensity scoring. Among other serious outcomes a search for possible cases

of VTE or ATE was conducted in the database based on computerized codes. The medical records for these potential cases were then abstracted and reviewed by trained personnel to adjudicate the cases. The protocol includes a validation (nested case control) study that was conducted as an essential part of this trial to better understand potential differences in the study cohorts. Finally, a total of 22,429 Yasmin initiators and 44,858 other OC initiators were identified and followed from 11 Jun 2001 to 30 Jun 2004.

Counts, incidence rates (IR), and rate ratios of VTE/ATE outcomes among Yasmin and Other OC initiators identified from date of launch of Yasmin through 30 June 2004 and followed for VTE/ATE outcomes from 11 Jun 2001 through 30 June 2004 are reported in as intention-to-treat population and as-treated population. The results are stratified by exposure (current use, recent use, past use, non-use). For the intention-to-treat analysis, a woman continued to contribute person-time within her initiating cohort even if she switched to another OC during the period of follow-up.

Based on an intention-to-treat analysis, there were 14,541 WY of follow-up available among Yasmin initiators and 19 confirmed ATE/VTE events in this cohort for an absolute IR of 1.3 events per 1,000 WY. The Other OC cohort provided 28,169 WY of follow-up and there were 40 confirmed ATE/VTE events during this follow-up for an absolute IR of 1.4 events per 1,000 WY. When the as-treated population was analyzed, there were 13,849 WY of follow-up for Yasmin users with 18 confirmed ATE/VTE events and an IR of 1.3. The Other OC cohort provided 28,860 WY of follow-up with 41 confirmed ATE/VTE events during this follow-up for an absolute IR of 1.4.

The crude rate ratio comparing the Yasmin cohort to the Other OC cohort was 0.9 for both the intention-to-treat and as-treated population (95% CI 0.5-1.6), consistent with a hypothesis of no difference in ATE/VTE incidence between the Yasmin and Other OC cohorts.

3.2 Ongoing BSP PASS Studies involving Yasmin

Two Post Authorization Safety Studies (PASS) are currently ongoing in Europe and the US for DRSP containing OCs.

3.2.1 Interim Results of the LASS Study

The Long-term Active Surveillance Study for Oral Contraceptives (LASS) is based on a follow up extension of the existing long-term EURAS cohorts with 47,799 OC users who were still in follow-up at the end of 2005. The EURAS study had followed OC users for one to five years. LASS will succeed EURAS and prolong the follow-up until the end of 2010. The following synopsis reflects the study status after three additional years of follow-up in May 2009.

The validated follow-up information for the Yasmin, LNG, and Other OCs cohort represents a total of 259,696 WY of observation: 72,752 WY for Yasmin, 72,217 WY for LNG and 114,050 WY for users of Other OCs. The corresponding OC exposure is as follows: 44,594 WY for Yasmin, 50,780 WY for LNG and 90,904 WY for users of Other OCs.

The main clinical outcomes of interest for the long-term follow-up are:

- death or hospitalization due to cardiovascular events (e.g., VTE, ATE, Congestive Heart Failure (CHF))
- breast cancer

Cardiovascular Outcomes

a) VTE

To date 196 confirmed VTE have been observed among current OC users. For Yasmin 46 events (incidence: 10.3 VTE/10,000 WY), for LNG 46 events (incidence: 9.1 VTE/10,000 WY) and for Other OCs 104 VTE (incidence: 11.4 VTE/10,000 WY) were confirmed. The Incidence Rate Ratios for Yasmin vs. LNG and Yasmin vs. Other OCs are 1.14 and 0.90, respectively. These rate ratios are almost identical with the ratios given in the final study report of the EURAS study (1.14 and 0.92, respectively). Cox regression analysis yielded adjusted (adjusted for age, BMI, duration of use, and VTE history) hazard ratios of 1.01 (95% CI, 0.65-1.57) and 0.80 (95% CI, 0.56-1.13) for Yasmin vs. LNG and Yasmin vs. Other OCs, respectively. These data further strengthen the EURAS conclusions that DRSP is not associated with a higher VTE risk compared to LNG.

b) ATE

To date 38 confirmed ATE have been observed among current OC users. For Yasmin 5 events (incidence: 1.1 ATE/10,000 WY), for LNG 14 events (incidence: 2.8 ATE/10,000 WY) and for Other OCs 19 events (incidence: 2.1 ATE/10,000 WY) were confirmed. Compared to the final EURAS data 2, 4, and 7 new cases were observed in the Yasmin, LNG, and Other OCs cohorts, respectively. The trend found in EURAS and in the 1st LASS interim analysis that the incidence rates are lowest in the Yasmin cohort seems to be stable. Cox regression analysis yielded adjusted (for adjusted for age, BMI, smoking and treated hypertension) hazard ratios of 0.42 (95% CI, 0.15-1.18) and 0.46 (95% CI, 0.17-1.24) for Yasmin vs. LNG and Yasmin vs. Other OCs, respectively.

c) Fatal cardiovascular outcomes

A total of four serious adverse cardiovascular events had a fatal outcome. All four events were associated with VTE or ATE. Overall, the total number of 4 fatal cases (3 in the LNG cohort and 1 in the Other OC cohort) is too small to assess cohort-specific risks.

d) Start of blood pressure lowering treatment

After study entry 208 Yasmin users (46.6/10,000 WY), 380 LNG users (74.8/10,000 WY), 528 users of Other OCs (58.1/10,000 WY) and 468 ex-users (women who had stopped OC use after

study entry for at least three months) started to use blood pressure lowering medication. Given the high statistical power of the study inferential statistics showed statistically significant differences for Yasmin vs. LNG, Yasmin vs. Other OCs, and Yasmin vs. all other progestins (incl. LNG). The adjusted hazard ratios were 0.66 (95% CI, 0.56-0.78), 0.73 (95% CI, 0.62-0.85), and 0.70 (95% CI, 0.60-0.81), respectively. The hazard ratios were adjusted for age and BMI. Furthermore, the ITT analysis showed also statistical significant differences between the cohorts. The potential impact of other important confounders will be analyzed in more detail at the end of the study.

Breast Cancer and Other Gynecological Cancers

a) Breast cancer

Overall, 65 breast cancer cases were diagnosed. Overall, the incidence rates for all three OC cohorts were approx. 2.5 cases/10,000 WY. The incidence rates for ex-users were slightly higher. These results yield no indication of an increased incidence of breast cancer that might be associated with Yasmin use. Furthermore, the results do not indicate that Yasmin promotes the growth of pre-existing breast cancers. Regarding tumor induction average follow-up times (~ 5 years) are still too short for robust conclusions.

b) Other gynecological cancers

As is typical for this age group, the most common other gynecological malignant neoplasm was cancer of the cervix uteri. The numbers for other cancers were too small for a meaningful analysis. Overall, 49 cervical cancer cases were diagnosed. The incidence rates for the Yasmin cohort were between 0.9 and 1.2/10,000 WY, for the LNG cohort between 1.7 and 2.6/10,000WY, and for Other OCs between 2.1 and 2.5/10,000 WY. Again, these results yield no indication of an increased incidence of cancer that might be associated with Yasmin use.

b) Other (non-gynecological) cancers

The numbers for other cancers were too small for a meaningful analysis.

Serious Adverse Events by Organ System

Overall, 10,018 serious adverse events were reported by the study participants (385.8 SAE/10,000 WY). This figure breaks down into 1,489 events for the Yasmin cohort (333.9 SAE/10,000 WY), 1,708 SAE for the LNG cohort (336.4/10,000 WY), 3,132 SAEs for the Other OC cohort (344.5 VTE/10,000 WY), and 3,307 SAE for women who had stopped OC use for at least 3 months (531.4 SAE/10,000 WY). The SAE rates are very similar for the 3 OC cohorts. The substantially higher reporting rates for ex-users are primarily a matter of SAEs in connection with pregnancy, delivery or puerperium.

Investigator's Conclusions on the Interim Results

The LASS results after three years of additional follow-up endorse - without exception - the results of the EURAS study. In addition, the results indicate that current users of Yasmin start less frequently treatment of high blood pressure compared to users of LNG and Other OCs.

3.2.2 Interim Results of the INAS study

This prospective, controlled, non-interventional, active surveillance, new user cohort study was designed to characterize the risk of use of oral contraceptives (OCs). The primary outcome of interest was cardiovascular events, in particular the incidence of venous thromboembolic events (VTE) but also arterial thromboembolic events (ATE) and arrhythmia during OC use with particular focus on YAZ, but also includes data on women using Yasmin. The study is being conducted as a phase 4 commitment for YAZ to the FDA and EMEA

The following synopsis of the "International Active Surveillance study of women taking oral contraceptives" (INAS OC) reflects the study status as of February 26, 2009. The study was started in the United States in August 2005. Until the recruitment stop in the US in July 2008, a total of 1,332 centers had recruited at least one patient. The targeted number of 10,000 YAZ users was reached by the end of the US recruitment phase.

Overall, a total of 52,219 US subjects were enrolled:

- 10,302 DRSP_{24d} (YAZ) users
- 3,982 DRSP_{21d}³ (Yasmin) users
- 37,935 users of other OCs

In addition, another 30,000 to 35,000 women are expected to be recruited in the European arm of the INAS OC study. Participating countries are: Austria, Germany, Italy, Poland, Croatia, and Sweden. European recruitment is planned for 2 years with a maximum follow-up phase of 4 years.

As of March 31, 2009, a total of 1,156 centers in Europe had agreed to participate (recruited centers) and 309 centers had recruited at least one patient (active centers). A total of 3,606 study participants had been recruited, of which 495 (13.7%) are YAZ users. At the end of the study, the estimated total exposure (US and Europe combined) to YAZ and non-DRSP-OCs is expected to be more than 32,000 and 130,000 WY, respectively. As the study has just started in the European countries, the available baseline database for this part of the study was small. Therefore, European baseline data have to be interpreted cautiously as they may change with more data.

³ In the US Yasmin[®], in Europe Yasmin[™] and Yasminelle[™]

Results: The validated follow-up information for the entire study population represents a total of 61,192 WY: 9,244 WY of exposure for YAZ, 4,621 WY for Yasmin, 35,433 WY for other OCs. 1,432 confirmed serious adverse events⁴ (SAEs) have occurred. SAE incidence rates for the three OC cohorts were approx. 200 events/10,000 WY. To date, 40 confirmed VTEs have occurred. For YAZ 8 events (incidence: 8.7 VTE/10,000 WY; 95% CI, 3.7 - 17.0), and for other OCs 24 events (incidence 6.8 VTE/10,000 WY, 95% CI, 4.3 - 10.1). Three events occurred in the Yasmin cohort (incidence 6.5 VTE/10,000 WY, 95% CI, 1.3 - 19.0).

Investigator's Conclusions on the Interim Results

The on-going INAS study interim results do not indicate an increased risk for VTE for Yasmin nor YAZ compared to users of Other OCs.

4. Overall Bayer Schering Pharma's Conclusions

The data from the Lidegaard et al¹ and the van Hylckama Vlieg et al² studies confirm some well-established overall association between OC use and VTE. However both of these studies conclude that OCs have a differential VTE risk based on the progestin component, including drospirenone. Based on the accompanying external expert opinions, by Prof S. Shapiro and Prof. S. Suissa, as well as our internal analysis, we have come to the conclusion that the comparison of drospirenone with levonorgestrel in the new publications was not valid due to the methodological issues discussed in this statement.

Also, the results of these retrospective studies are not consistent with the large amount of data generated in clinical and post-marketing^{3,4} trials. In the completed Post Authorization Safety Studies on the cardiovascular safety of Yasmin (EURAS OC³ and Ingenix⁴ Yasmin study) completed as phase 4 commitments to EMEA and the FDA, the VTE and ATE rates for Yasmin were found to be similar to those observed with other OCs. While Bayer sponsored these two large observational comparative cohort studies, the study concept, conduct, analysis and reporting were performed by two different independent investigator groups, using two different methodologies and in two geographically different populations. Both studies were specifically designed - after extensive discussion with European and US Health Regulators - to achieve balance between the cohorts, e.g., by controlling for confounding factors and were sufficiently powered to assess differences between preparations. The results of both studies were assessed with a blinded medical adjudication process. Both studies were also overseen by independent Data Safety Monitoring Boards and all case reports were submitted to Health Authorities for review.

The results from EURAS³ and Ingenix⁴ are highly concordant. They were obtained from two prospective studies designed in collaboration with the EMEA and the US FDA, including final protocol approvals (EMEA for EURAS, US FDA for Ingenix). These two studies support the recent goal of regulatory authorities to achieve high quality Post Authorization Safety Studies (PASS). In this context, any serious challenge to the validity of the conclusions from EURAS³

and Ingenix⁴ should come only from trials that effectively overcome and control adequately for the shortcomings of the prior generation of epidemiologic studies, preferably in the form of prospective trials.

In the ongoing PASS studies (LASS and INAS), to date the VTE and ATE rates with Yasmin are also similar to those observed with other OCs.

The entirety of the data as described in this Expert Statement substantiate that Yasmin is a safe and efficacious OC, when taken as prescribed. The risk-benefit assessment for Yasmin remains unchanged.

It is therefore the respectful opinion of Bayer Schering that neither the Lidegaard et al¹ or the van Hylckama Vlieg et al² studies achieve the level of evidence that would be required to challenge the results from the EURAS³ and Ingenix⁴ trials. To do so would risk compromising the very principles behind PASS programs, and all of the significant insights that have been gained in recent years through these initiatives.

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List of abbreviations

AC	Advisory Council
ADR	Adverse Drug Reaction
AE	Adverse Event
AMI	Acute Myocardial Infarction
AT	As treated
ATE	Arterial Thromboembolism
BMI	Body Mass Index
CVA	Cerebrovascular Accident
DRSP	Drospirenone
DVT	Deep Venous Thrombosis
EE	Ethinyl Estradiol
EURAS	European Active Surveillance [Study]
HR	Hazard Ratio
ITT	Intention to treat
LNG	Levonorgestrel
OC	Oral Contraceptive
PE	Pulmonary Embolism
NOHC	Non-oral Hormonal Contraceptive
PP	Per Protocol
(S)ADR	(Serious) Adverse Drug Reaction
(S)AE	(Serious) Adverse Event
TE	Thromboembolic Event
TIA	Transient Ischemic Attack
VTE	Venous Thromboembolism
VST	Venous Sinus Thrombosis
WY	Women Years

ZEG

Centre for Epidemiology & Health Research Berlin (acronym for the German term “Zentrum für Epidemiologie & Gesundheitsforschung”)

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10.2 Appendix 2: Sponsor's Clinical Expert Statement on 2011 BMJ Publications (US PharMetrics study [Jick and Hernandez 2011] and the UK General Practice Research Database study [Parkin et al., 2011])

The following was initially submitted to the FDA in April 2011 in response to the 2011 BMJ publications.



CLINICAL EXPERT STATEMENT

BAYER SCIENTIFIC REVIEW OF TWO MANUSCRIPTS PUBLISHED IN THE APRIL 24, 2011 ISSUE OF THE BMJ

Author: Dr. Leo Plouffe, Jr

Date: April 29, 2011

Dr. Ilka Schellschmidt

1.	INTRODUCTION	3
2.	UNITED STATES CLAIMS DATA (PHARMETRICS) STUDY.....	4
2.1	Abstract (reproduced integrally from the BMJ publication).....	4
2.2	Bayer Internal Scientific Assessment	5
2.2.1	<i>Issues with the PharMetrics database given the study objective.....</i>	<i>5</i>
2.2.2	<i>Concerns with the epidemiologic methods and the statistical approach.....</i>	<i>7</i>
2.2.3	<i>Issues with terms definitions.....</i>	<i>9</i>
2.3	Interpreting the current study from a clinical perspective and in the context of existing body of literature	12
2.4	Bayer's Overall Assessment of the Manuscript.....	15
3.	UK GENERAL PRACTICE RESEARCH DATABASE STUDY	16
3.1	Abstract (reproduced integrally from the BMJ publication).....	16
3.2	Bayer Internal Scientific Assessment	17
3.2.1	<i>Issues with the GPRD given the study objective.....</i>	<i>17</i>
3.2.2	<i>Concerns with the epidemiologic methods</i>	<i>18</i>
3.3	Interpreting the current study from a clinical perspective and in the context of existing body of literature	20
3.4	Bayer's Overall Assessment of the Manuscript.....	20
4.	BAYER'S OVERALL CONCLUSION	21
5.	REFERENCES	22
	APPENDIX 1 – BAYER COMMENTARY ON THE US PHARMETRICS DATABASE.....	24

1. Introduction

The purpose of this Expert Statement to Regulatory Authorities from Bayer is to provide Bayer's internal scientific review and interpretation of two recently published studies in the 24 April 2011 issue of the British Medical Journal:

- ***Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data.*** Jick SS and Hernandez RK. BMJ 2011;340:d2151¹
- ***Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database.*** Parkin L, Sharples K, Hernandez RK, Jick SS. BMJ 2011;340:d2139²

The authors compare the risk of idiopathic venous thromboembolism (VTE) in users of levonorgestrel (LNG)-containing combined oral contraceptives (LNG-COCs) to those using drospirenone (DRSP)-containing combined oral contraceptives (DRSP-COCs) and conclude, in each manuscript, based on their interpretation of the study results, that DRSP-COCs carry a higher risk of VTE than LNG-COC^{1,2}.

Overall, Bayer's analysis of these manuscripts identifies significant concerns about the reliability of the findings and conclusions presented by the authors, especially in the context of the extensive body of existing literature on the subject³⁻⁵.

Given the already large and robust scientific body of evidence, in Bayer's opinion, these two studies do not change the overall assessment about the safety of Bayer's DRSP-COCs. Bayer re-affirms that the overall body of available scientific evidence continues to provide support that the risk of developing venous thromboembolism, or blood clots, in women using DRSP-COC is comparable to other combination birth control pills studied, including those containing LNG.

In addition to its internal scientific review, Bayer is seeking external scientific consultation on these manuscripts. It is Bayer's intent to provide this assessment as soon as it becomes available.

We present here Bayer's latest internal scientific assessment of each manuscript, and Bayer's overall interpretation relative to the overall benefit-risk of DRSP-COCs.

2. United States Claims Data (PharMetrics) Study

2.1 Abstract (reproduced integrally from the BMJ publication)

Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data

Jick SS and Hernandez RK. BMJ 2011;340:d2151

ABSTRACT

Objective To compare the risk of non-fatal venous thromboembolism in women receiving oral contraceptives containing drospirenone with that in women receiving oral contraceptives containing levonorgestrel.

Design Nested case-control and cohort study.

Setting The study was based on information from PharMetrics, a United States based company that collects information on claims paid by managed care plans.

Participants The study encompassed all women aged 15 to 44 years who received an oral contraceptive containing either drospirenone or levonorgestrel after 1 January 2002. Cases were women with current use of a study oral contraceptive and a diagnosis of venous thromboembolism in the absence of identifiable clinical risk factors (idiopathic venous thromboembolism). Up to four controls were matched to each case by age and calendar time.

Main outcome measures Odds ratios comparing the risk of non-fatal venous thromboembolism in users of the two contraceptives; incidence rates and rate ratios of nonfatal venous thromboembolism for users of each of the study contraceptives.

Results 186 newly diagnosed, idiopathic cases of venous thromboembolism were identified in the study population and matched with 681 controls. In the case-control analysis, the conditional odds ratio for venous thromboembolism comparing use of oral contraceptives containing drospirenone with use of those containing levonorgestrel was 2.3 (95% confidence interval 1.6 to 3.2). The incidence rates for venous thromboembolism in the study population were 30.8 (95% confidence interval 25.6 to 36.8) per 100 000 woman years among users of oral contraceptives containing drospirenone and 12.5 (9.61 to 15.9) per 100 000 woman years among users of oral contraceptives containing levonorgestrel. The age adjusted incidence rate ratio for

venous thromboembolism for current use of oral contraceptives containing drospirenone compared with those containing levonorgestrel was 2.8 (2.1 to 3.8).

Conclusions The risk of non-fatal venous thromboembolism among users of oral contraceptives containing drospirenone seems to be around twice that of users of oral contraceptives containing levonorgestrel, after the effects of potential confounders and prescribing biases have been taken into account.

2.2 Bayer Internal Scientific Assessment

Some findings from this study are concordant with well established data about the VTE risk associated with COC use³⁻⁷. For example, the authors describe an increased risk of VTE with age, for both LNG-COCs and Yasmin. However, the fact that some analyses from this study align with those from previously published studies does not de facto validate the overall conclusions proposed by the authors.

Bayer's predominant concerns with the reliability of the findings from this study are based on the appropriateness of the PharMetrics database given the study objectives. Additionally, there are concerns with the epidemiologic methods and the statistical approach as well as with the issue with definition of terms.

2.2.1 Issues with the PharMetrics database given the study objective

From the onset, the PharMetrics database presents significant limitations as a source of data to assess the differential risk of VTE among various COCs, limitations that are considered difficult to overcome, especially if no further validation through clinical records is attempted. The shortcomings of any study based entirely on the PharMetrics database include the inability to account for important confounders, that is factors that are associated with both patient selection and the primary outcome, as well as the inability to validate the primary outcome. Given the nature of this study within this database any association detected cannot be considered causal.

The authors describe in the manuscript that this database has been used previously to examine differential risk of idiopathic VTE among various female contraceptives. From Bayer's review, however, it appears that one of the authors (SS Jick) has been involved in all prior publications on this particular issue utilizing the PharMetrics database. It appears likely that prior publications by Dr. Jick et al., based on the PharMetrics database, may suffer from the same limitations^{8,9}. One example of the level of uncertainty associated with studies on the current topic, based on the PharMetrics database, is the broad range of values reported for the incidence rate of idiopathic VTE with LNG-COC, over the time period from 2000 to 2008 (Table 1). Reported incidence rates for VTE with LNG-COC range from 12.5/100,000 Women-Years (95% CI 9.6-15.9) in the current study¹, to 38.0/100,000 WY (95% CI 23.4-61.7)⁹, a 3-fold difference. These discordant rates are nonetheless based on apparently comparable cohorts from the same data source over overlapping time intervals. While

the current study included both 20 and 30 µg ethinyl estradiol (EE) preparations compared to the two prior studies that included only 30µg EE preparations, it is unlikely that this alone could account for this 3-fold variation in VTE event rates for LNG-COC. Such wide fluctuations more likely reflect the inherent weaknesses of the PharMetrics database in conducting studies on the risk of VTE with COCs.

TABLE 1 Jick et al. - Studies on VTE and contraceptives – Idiopathic VTE event rates for LNG subjects only from the PharMetrics Database

Study	VTEs Number of Cases	Database	Timeframe	Event Rate (100,000 WY)	Event rate (100,000 wy) (95% CI)
Jick et al., Contraception 73 (2006) 566-70 ⁸	70	PharMetrics	January 2000 – March 2005	LNG-30mcg 27.1	21.1-34.3
Jick et al., Contraception 81 (2010), 16-21 ⁹	16	PharMetrics	April 1 2002 – March 2006	LNG-30mcg 38.0	23.4 – 61.7
Jick et al., BMJ 2011; 340:d2151 ¹	65	PharMetrics	Jan 1 2002 – Dec 31 2008	LNG-(20 or 30mcg) 12.5	9.6 – 15.9

Bayer is very familiar with the PharMetrics database, primarily as a source database for pharmaco-economic research. Further background information on the PharMetrics database is provided in Appendix 1. There are key structural elements in the PharMetrics database that introduce significant confounders in the study of a rare clinical event that is known to be linked to treatment duration and risk factors, such as VTE.

As stated above, the PharMetrics database has significant limitations to adequately account for key confounding factors. Clinical information such as weight and BMI, while relevant for risk of developing VTE, do not exist in the PharMetrics database. Codes relevant to VTE risk such as personal history of VTE, past history of cancer, family history of VTE, previous use of COC, thrombophilia, obesity, and hypertension will exist only when the treating Health Care Professional (HCP) deems it to be an important element of the current medical consultation but none of these are documented systematically. The database allows a maximum of 3 diagnoses only for a given patient encounter. There are no specific criteria within the database to guide when these codes are applied, or the context in which they are applied.

In the PharMetrics database, a subject can enter the database under one health plan and then remain in the database, under the same patient identifier or a new one, if she changes to a plan that also submits data to PharMetrics. It is possible for a subject to

enter, leave, and reenter the database multiple times, either under the same patient identifier or multiple ones. It is customary, when using the PharMetrics database, to control appropriately to make sure that the subjects being incorporated in the cohort for study were continuously eligible (for health care coverage by one or more of the participating plans) for the entire study period. This is generally clearly reflected in the Methods section of studies using the PharMetrics or other US Claims database, stating that “subjects were continuously eligible”. It does not appear that this approach was followed in the current study. This would be a source of bias that would compromise drawing meaningful conclusions.

While the authors do acknowledge some of these limitations of the PharMetrics database in their discussion, they propose that additional data explorations within their study and a companion manuscript do not suggest that these limitations are consequential. Bayer disagrees with this approach. Risk factors for VTE have long been established and acknowledged in the label of COCs by Regulatory authorities around the world and by prescribing physicians as highly relevant for their daily contraceptive counseling. These are deemed consequential and studies into this issue should allow for a robust assessment of these contributory factors, including direct access to clinical information, as it cannot be excluded that there is a differential prescribing with regard to these factors. The PharMetrics database does not permit a validation, and the authors did not attempt to access clinical information for the cases and controls identified in their study.

The challenge of accurately identifying patients with true VTE from retrospective studies in databases without performing a validation by medical chart review is widely acknowledged. In the current analysis, the ascertainment of cases is based purely on the information available within the database. It is recognized that objective testing for DVT confirms only 20-30% of suspected patients referred for testing¹⁰. While the authors attempt to use some criteria (e.g. patient must have received anticoagulation therapy - without specifying the duration) to reduce the likelihood of including “false positive” cases, anticoagulation by itself does not confirm the diagnosis (e.g. some guidelines recommend anticoagulation if there is a positive d-dimer). Despite these issues, based on the manuscript, it appears that no attempt at clinical chart review was undertaken. Bayer views this as a significant limitation of the current study, calling into question the reliability of its conclusions.

In summary, Bayer does not believe that the US PharMetrics database, without additional clinical validation, is an appropriate data source for a study comparing the risk of VTEs among COCs. In this context, Bayer views the results of the current study and the conclusions reached by the authors as unreliable.

2.2.2 Concerns with the epidemiologic methods and the statistical approach

A significant concern with the publication is that neither the data set, nor the methodology used by the authors is adequately described. How the overall cohort was selected is not clear, and there is no chart indicating how the exclusion criteria

molded the overall cohort. With respect to the nested case-control, Table 1 of the publication provides characteristics of the selected non-cases (controls) by exposure, but, inexplicably, does not provide characteristics of the cases.

Given that the risk of VTE with COCs is not constant over time (known to be higher for new users during the first year of use) the methodology employed in a non-randomized study to avoid confounding is critical. In randomized trials of treatment effect, balance of baseline characteristics between treatments is ensured, on average, by randomization. In well-designed cohort studies, baseline balance between treatment groups for risk factors (including new user status) can be established and demonstrated using propensity methods⁴. In a case-control design, baseline balance between treatments is not established or demonstrated. Instead, the means for dealing with confounding is modeling of the outcome using conditional logistic regression applied to the cases and to the selected non-cases (controls). The result, in turn, is heavily dependent on the method used for selection of the controls. The authors of the publication used “risk set sampling” to select the controls. In risk set sampling the controls corresponding to a case are selected from among those individuals who were at risk at the time of the index date (in this case, those under current treatment at the time of the index date), and the probability that an individual is selected as a control is proportional to the exposure time (time on treatment) within the follow-up period contributed by that individual. It is likely, however, that because of different patterns of use that change over time, the exposure person-time contributed by the DRSP-COC users is distributed differently from the exposure time contributed by the LNG-COC users, within the same follow-up time. It is doubtful that conditional logistic regression can adequately adjust for this.

Another consideration is that it is customary, in the design of US claims database studies, including those from PharMetrics, to decide a priori what duration of pre-index data is wanted and this criterion is then applied consistently for all subjects. For example, if it is decided to study a cohort with 6 months of medical data prior to an index event, all subjects in the cohort must have 6 months of medical data prior to the index event. If a subject has less than 6 months of data, they are excluded, as was done in the study. If however, more than 6 months of data prior to the index event is available for a given subject, the data beyond the 6 months period should not be considered. It appears that this approach was not used in the current study. This obviously applies for studies relying exclusively on the database. The authors report excluding subjects with a number of predisposing factors for VTE, including a history of cancer and autoimmune disorders based on the totality of the information available for that subject within the database. This means that for cases and controls, the period of data considered from the database may have ranged from a minimum of 6 months of data for some subjects (required for all subjects in the study, per Methods), but potentially ranging up to several years for others. This is a further source of uncertainty.

The authors describe the study cohort in the abstract as encompassing “all women aged 15 to 44 years who received an oral contraceptive containing either drospirenone or levonorgestrel” while in the method description this is changed into women who

should have filled at least one prescription for a study drug after 1 January 2002 and who fulfilled any of the many exclusion criteria applied. However, the specific procedures for defining these “current use” cohorts are not adequately described and therefore do not allow for a full review. To enable the reader to interpret the results from these studies, full information on the selection of the study cohort should be given.

It is common in publications to provide a flow chart indicating how different selection criteria influence the resulting study cohort and also to give a full description on the distribution of age and exposure of the exclusions as well as of the resulting study cohorts. There are reasons to assume that the exclusion criteria (e.g., cancer, renal failure, chronic cardiovascular disease, inflammatory diseases and autoimmune diseases) would be strongly influenced by a woman’s age and also her dwell time in the database.

The same lack of transparency applies to the description of cases and controls. For example, while Table 1 in the manuscript provides separate demographic information for controls on LNG-COC or DRSP-COC, this information is not provided for the cases. This would be valuable information in order to assess differences between cases using either DRSP-COC or LNG-COC. From the information provided for the control groups, it is evident that women using DRSP-COCs were more likely to be younger, were more likely to have a shorter duration of oral contraceptive use, were more likely to be new vs. continuous users of COCs, and more likely to have a record of a menstrual disorder than users of LNG COCs. Similar insights into the cases would be extremely valuable to further analysis of this study. Given that the DRSP-COC cohort tends to be younger, and based on the pattern seen in prior studies, failing to control adequately for prior use would introduce a strong bias against the DRSP-COC cohort.

Overall, the methodological and statistical concerns listed above compound the inherent challenges of using the US PharMetrics database to achieve the study objective of comparing the risk of VTEs between DRSP-COC and LNG-COC users.

2.2.3 Issues with terms definitions

In addition to the challenges of identifying true VTE cases from an administrative database, the authors further restrict their study to “idiopathic” cases. The definition for “idiopathic VTE” varies across the literature, including between manuscripts from one of the lead authors (S. Jick) (for an overview of selection of idiopathic cases by S. Jick please refer to Table 2). This introduces an additional source of bias in interpreting the data. In the current study, it appears that an attempt was made to remove disease-related risk factors, but not intrinsic ones. A family history of VTE is a widely acknowledged risk factor for VTE; it appears that such a family history should exclude a patient from the idiopathic VTE category. However, as previously

noted, information on a family history of VTE is not available within the PharMetrics database. This is viewed as a significant inconsistency.

TABLE 2 – Criteria used to exclude subjects from inclusion into “idiopathic cases” category reported by Jick et al in studies of LNG-COC

Exclusion criteria	2006 ⁸	2010 ⁹	PharMetrics 2011 ¹	GPRD 2011 ²
Important lower-limb injury	X		X	
Major injury				X
Prolonged immobility				X
Invasive / major surgery	X		X	X
Recent (within 90 days) major surgery		X		
(Severe) trauma	X	X	X	
Epilepsy		X		
Pregnancy	X	X	X	X

It is also unclear as to how systematically a personal history of VTE was ruled-out since only 6 months of medical history was requested prior to the index date (date of event) but for some subjects, a much longer period of data may have been ascertained (as discussed before). The PharMetrics database contains data back to 1995; it is unclear from the manuscript if entries in the database were examined prior to 2002 to identify any potential prior episode of VTE, and if so, how this was performed. While it is acknowledged by Bayer that it is unlikely that women with a prior history of VTE would have been started on a COC, in the context of US clinical practice, this cannot be ruled-out and may be an additional source of bias.

Beyond the criteria used to exclude VTE cases from the “idiopathic” group (Table 2), the authors also excluded up-front a number of individuals from the study cohort on the basis of underlying medical conditions (Table 3). Some of these conditions are widely acknowledged as risk factors for VTE (e.g. history of cancer), but many of the other baseline exclusion criteria are not generally acknowledged as risk factors for VTE (e.g. autoimmune disorders). The authors do not provide a justification for excluding these patients. As previously noted, the presence or absence of these diagnoses is unreliable as some of these conditions may have occurred prior to a subject’s inclusion in the database, therefore not being captured, or are unevenly ascertained as unequal time periods among subjects was apparently considered for ascertainment (see above). Since women in the LNG-COC cohorts are reported to be older than those in the DRSP-COC cohort, and since the prevalence of many of the excluded conditions increases with increasing age, it is also reasonable to assume that more LNG-COC cases were excluded than were DRSP-COC cases.

TABLE 3 – Criteria used to exclude subjects from study cohorts reported by Jick et al in studies of LNG-COC

Exclusion criteria	2006 ⁸	2010 ⁹	PharMetrics 2011 ¹	GPRD 2011 ²
Description in study methodology section*				
Chronic cardiovascular disease			X	
<i>Myocardial infarction</i>				X
<i>Stroke</i>				X
<i>Other cardiovascular disease</i>				X*
<i>Treated hypertension</i>				X
Any history of cancer (excluding nonmelanoma skin cancer)	X		X	X
Renal failure	X		X	X (chronic)
Inflammatory or autoimmune conditions	X		X	
<i>Ulcerative and other spondylopathies</i>				X
<i>Lupus erythematosus</i>				X
<i>Rheumatoid arthritis</i>				X
<i>Ankylosing spondylitis and other spondylopathies</i>				X
<i>Psoriatic arthritis</i>				X
Previous VTE				X
Treated hyperlipidaemia				X
Type 1 diabetes				X
Cystic fibrosis				X
Injection drug use				X
Coagulation defects				X
Previously used oral anticoagulation (considered nonidiopathic)		X		

*** Detailed exclusion criteria**

2006⁸ - Well documented important clinical risk factors for VTE present in the 3 months prior to the index date

2010⁹ - Exclusion applied only to cases, to rule-out non-idiopathic cases – Stated as “strong risk factors for VTE”

PharMetrics 2011¹ – “if important clinical risk factors for VTE were present in the 90 days prior to index date”

GPRD 2011² – “Women were excluded if they had a recorded history of risk factors for VTE, as well as other conditions which might influence decisions about prescribing of oral contraceptives”

The focus on “idiopathic” cases ultimately led to the exclusion of a majority of the VTE cases (61%) available for analysis in the study. At the same time, given the nature of the information in the PharMetrics database, it is likely that women with

significant underlying personal factors or family history were not excluded from the “idiopathic group”. In addition, an attempt to focus only on “idiopathic cases” may have introduced further bias in the selection/confirmation of cases.

Additional issues arise with the definitions of new users, starters and restarters. Current COC use was determined by a recorded claim for a COC prescription whose filled use extended to within 30 days before the index date or beyond the index date. A new episode of COC use (versus continuous use of a COC) was based on no recorded use (and availability of >4 months data) or a gap of ≥ 100 days from a prior COC prescription. Unfortunately, given the limitations of the database, as outlined above, and these definitions, duration of use cannot accurately be determined and may lead to starters or restarters being compared with long term users.

2.3 Interpreting the current study from a clinical perspective and in the context of existing body of literature

It is Bayer’s opinion that specific elements of this study make it very challenging to relate the findings to the existing body of literature. Bayer’s reasons for this assessment are outlined below. Whenever possible, correlations are drawn relative to the existing body of scientific evidence.

The authors limit the reporting and analyses to “idiopathic” cases (i.e. cases without apparent risk factors). While one of the authors (SS Jick) has applied the same approach to prior studies comparing the risk of VTE among female contraceptives, this approach is different from the larger body of literature on COCs that reports on all cases of VTE. Limiting the report and analyses to “idiopathic” cases, at the very least, makes it difficult to relate the current findings to the existing literature.

The authors explain their rationale for focusing on “idiopathic” VTEs. It is Bayer’s position that at the very least, the authors should have reported on all cases of VTE, followed by subset analyses. This approach would reflect clinical reality and be much more informative and of great assistance in better understanding the reported findings from this study. In the end, the relevance of data generated through the analysis of “idiopathic” cases only in the broader context of guiding clinical practice has yet to be established¹¹.

A puzzling finding from this study is the very low VTE event rate reported, even when considering that only “idiopathic” cases of VTE are presented. This applies particularly to the LNG-COC users, even when comparing to other manuscripts reporting only on “idiopathic” VTE cases^{8,9} (different rates published by SS Jick are presented in Table 1 and 4). It is unclear why such discrepancies should exist, given that many of the data have been generated from the same database, at overlapping time intervals, with reportedly a similar methodological approach.

TABLE 4 Jick et al., studies on VTE and contraceptives – Idiopathic VTE event rates for LNG subjects only

Study	VTEs Number of Cases	Database	Timeframe (months)	Event Rate (100,000 WY)	Event rate (100,000 WY) (95% CI)
Jick et al., Contraception 73 (2006) 566-70 ⁸	70	PharMetrics	Jan 2000 – Mar 2005	LNG-30mcg 27.1	21.1-34.3
Jick et al., Contraception 81 (2010), 16-21 ⁹	16	PharMetrics	Apr 1 2002 – Mar 2006	LNG-30mcg 38.0	23.4 – 61.7
Jick et al., Contraception 81 (2010), 16-21 ⁹	50	Marketscan	Apr 1 2002 – Dec 31 2007	LNG-30mcg 19.9	15.1-26.3
Jick et al., BMJ 2011; 340:d2151 ¹	65	PharMetrics	Jan 1 2002 – Dec 31 2008	LNG-(20 or 30mcg) 12.5	9.6 – 15.9
Parkin et al., BMJ 2011; 340:d2139 ²	44	GPRD	May 1 2002 – Sep 30 2009	LNG-30mcg 9.1	6.6 – 12.2

Bayer also performed an extrapolated analysis of overall VTE event rates, based on the data included in the manuscript that 61% of cases were non-idiopathic. This analysis also shows a markedly lower overall rate of VTE for LNG-COC users, when compared to the existing literature^{3-5, 12, 13}; it is in the lower range of rates reported in other studies for DRSP-COC (Table 5).

TABLE 5 Bayer internal calculations around VTE event rates from PharMetrics database study¹. Rates reported as 10,000 Women Years

Exposure	Cases N=186	Women Years	Incidence Rate per 10,000 WY Idiopathic only	95% Confidence Interval (per 10,000 WY) Idiopathic only	Extrapolated Total Rate [Idiopathic (39%) + Non-Idiopathic Rate (61%)] (95% C.I.)
Drospirenone (EE 30 mcg only) Exposed					
Age <30	63	253,895	2.48	1.91 – 3.17	6.4 (4.9-8.1)
Age 30 – 39	42	107,701	3.90	2.81 – 5.27	10.0 (7.2-13.5)
Age 40 –44	16	31,248	5.12	2.93 – 8.32	13.1 (7.5-21.3)
Levonorgestrel (EE 20 or 30 mcg) Exposed					
Age <30	14	259,522	0.54	0.29 – 0.91	1.4 (0.8-2.3)
Age 30 – 39	35	187,017	1.87	1.30 – 2.60	4.8 (3.3-6.7)
Age 40 –44	16	75,284	2.13	1.21 – 3.45	5.5 (3.1-8.8)

These findings raise questions about bias, including the selection of study participants into the study cohorts. This could be a reason for these unusually low incidence rates, especially among LNG-COC users. In this context, it is unclear whether or not the reported difference in the rate of “idiopathic” VTE between LNG-COC and DRSP-COC users is the result of:

- A higher VTE event rate with DRSP-COC, as concluded by the authors
- An unusually low VTE event rate among LNG-COC users
- Some combination of these that may have been a consequence of how the study cohort was created (Table 4).

In summary, Bayer finds it very difficult to interpret the reported results of the current study in the context of the existing literature on the subject³⁻⁷. This is related in part to the presentation of data only for “idiopathic” VTE cases. The data for VTE incidence among LNG-COC users differ markedly from those reported to date, without any obvious explanation. In this context, the absence of any other comparator

group (besides LNG-COC or DRSP-COC), either non-users or users of COCs with other previously studied progestins makes it difficult to interpret the results of the current study in the broader context of the existing literature.

2.4 Bayer's Overall Assessment of the Manuscript

Bayer's analysis of this manuscript raises significant concerns about the reliability of the findings and the conclusions reached by the authors. This opinion is based primarily on the architecture and dynamics of the PharMetrics database as the sole source of data for the current study. Key elements of how the data were captured and analyzed amplify the concerns around the reproducibility of the findings from the current study. Finally, the lack of an additional comparator (non-user or another COC with a different progestin) within the study, and reporting exclusively on "idiopathic" cases make it very challenging to evaluate the findings of the current study in relationship to the existing body of evidence on this topic.

3. UK General Practice Research Database Study

3.1 Abstract (reproduced integrally from the BMJ publication)

Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database

Parkin L, Sharples K, Hernandez RK, Jick SS. *BMJ* 2011;340:d2139

ABSTRACT

Objective To examine the risk of non-fatal idiopathic venous thromboembolism in current users of a combined oral contraceptive containing drospirenone, relative to current users of preparations containing levonorgestrel.

Design Nested case-control study.

Setting UK General Practice Research Database.

Participants Women aged 15-44 years without major risk factors for venous thromboembolism who started a new episode of use of an oral contraceptive containing 30 µg oestrogen in combination with either drospirenone or levonorgestrel between May 2002 and September 2009. Cases were women with a first diagnosis of venous thromboembolism; up to four controls, matched by age, duration of recorded information, and general practice, were randomly selected for each case.

Main outcome measures Odds ratios and 95% confidence intervals estimated with conditional logistic regression; age adjusted incidence rate ratio estimated with Poisson regression.

Results 61 cases of idiopathic venous thromboembolism and 215 matched controls were identified. In the case-control analysis, current use of the drospirenone contraceptive was associated with a threefold higher risk of non-fatal idiopathic venous thromboembolism compared with levonorgestrel use; the odds ratio adjusted for body mass index was 3.3 (95% confidence interval 1.4 to 7.6). Subanalyses suggested that referral, diagnostic, first time user, duration of use, and switching biases were unlikely explanations for this finding. The crude incidence rate was 23.0 (95% confidence interval 13.4 to 36.9) per 100 000 woman years in current users of drospirenone and 9.1 (6.6 to 12.2) per 100 000 woman years in current users of levonorgestrel oral contraceptives. The age adjusted incidence rate ratio was 2.7 (1.5 to 4.7).

Conclusions These findings contribute to emerging evidence that the combined oral contraceptive containing drospirenone carries a higher risk of venous thromboembolism than do formulations containing levonorgestrel.

3.2 Bayer Internal Scientific Assessment

Bayer has significant concerns with the reliability of the findings from this study. These concerns relate to the appropriateness of the GPRD for the particular comparison at hand, between LNG-COC and DRSP-COCs. There are further significant issues with some key elements of the methodology used by the authors.

3.2.1 Issues with the GPRD given the study objective

The GPRD is one of many large health care databases that include some demographic data, information on prescription medications, medical diagnoses, hospital stays and deaths. As such, it is fully appropriate to support explorations, such as the current nested case-control study in studying a differential for VTE among different COCs. It is still deemed essential to complement the information from the database with information obtained from clinical records, if one wishes to achieve an appropriate level of quality information.

A prerequisite for a study of this type is that there is an adequate level of exposure in the database of the drugs to be compared. One major challenge to using the GPRD to address the current study objective is that the COC use pattern in the UK is characterized by a majority of women using LNG-COCs. The market share of the only available DRSP-COC in the UK (Yasmin) is markedly lower than the market share for LNG-COCs, and much lower than it is in the rest of Europe and the USA. Yasmin is frequently under formulary restrictions in the UK (on a geographical basis, for economic reasons) and therefore, its use in clinical practice in the UK is likely to differ markedly, in terms of the characteristics of candidate patients and users, from the broadly used LNG-COC. This formulary restriction status makes it extremely unlikely that Yasmin is ever prescribed as a first-line COC; beyond this, the use is determined through regional access panels that regulate the criteria that dictate the circumstances when Yasmin can be prescribed and are associated with a strong disincentive for HCPs to prescribe Yasmin. This set of circumstances, unique to the UK, and different between regions within the UK, challenges the generalizability of the findings of this study to the entire UK population as well as to other countries.

The challenge of accurately identifying patients with VTE from retrospective studies in databases without performing a validation by medical charts review is widely acknowledged. As Bayer has already stated, studies based on the GPRD should be complemented by access to full medical records, for the study of a rare and complex event such as VTE. In the current publication, the ascertainment of cases is based on

the information available within the database. While the authors have applied some criteria to reduce the likelihood of including “false positive” cases such as excluding women who did not have a recorded treatment with an anticoagulant (without specifying the duration), and those who continued to receive prescriptions for oral contraceptives after the presumed event, an effort at validating the VTE cases was attempted in less than half of the cases. The authors report requesting clinical charts for about 65% (42/65) of cases and actually reviewing a total of 31 out of 65 cases. Based on the validation attempt, a total of 4 cases out of the 31 reviewed cases were excluded from the analysis (12.9%). No attempt to adjust the incidence rates due to results from the partial validation is done. Therefore, the analyses are primarily based on the review of the information collected within the administrative database.

The authors report 27 cases of deep vein thrombosis (DVT), 34 cases of pulmonary embolism (PE), and no instance of subject(s) having been diagnosed with both events. This is very different than the usually reported predominance of DVT compared to PE, with DVTs usually accounting for 60-75% of all cases of VTE. It is also customary to identify a subset of patients with both a diagnosis of VTE and PE, an event not described here; the absence of such case may reflect the small number of total cases ascertained and the unusual characteristics of the population being studied. Such a finding would align with the unusual market position of Yasmin in the UK, as outlined above. The overall discordance from the general literature in the ratio of VTE/PE reported in his study raises a number of questions, including significant issues in the ascertainment of cases.

3.2.2 Concerns with the epidemiologic methods

Several issues arise from the manner in which the authors present their data. The authors describe the study cohort as encompassing “women aged 15 to 44 years without major risk factors for venous thromboembolism who started a new episode of an oral contraceptive containing 30 µg oestrogen in combination with either drospirenone or levonorgestrel”. However, the methods applied when selecting the study population are not fully described. It is common in publications to provide a flow chart on how different selection criteria influence the resulting study cohort and also to give a full description on the distribution of age and exposure of the exclusions as well as of the resulting study cohorts. There are reasons to assume that the exclusion criteria (e.g., cancer, renal failure, chronic cardiovascular disease, inflammatory diseases and autoimmune diseases) would be strongly influenced by a woman’s age and also her dwell time in the database.

The same lack of transparency adheres to the description of cases and controls. For example, while Table 1 in the manuscript provides information for cases and controls, this information is not provided by COC use (i.e., for LNG-COC or DRSP-COC users, both for cases and controls). This would be essential information to assess differences between cases using either DRSP-COC or LNG-COC especially in light

of the specific clinical practice in the UK which is likely to differ markedly, in terms of candidate users for Yasmin compared to the more broadly used LNG-COC.

The information about past COC use is completely ignored in the analyses. Given that the DRSP-COC cohort tends to be younger, and based on the pattern seen in prior studies, failing to control adequately for prior use would introduce a strong bias against the DRSP-COC cohort.

A cornerstone of the study is the identification of exposure status, to either DRSP-COC or LNG-COC. Exposure status is based on receipt of a prescription by the study subject. The study does not require the prescription to be filled to qualify a subject as “exposed”. This may be a source of bias in the interpretation of the data, especially given the likely differences in the dynamics of patients filling out prescriptions for LNG-COCs vs DRSP-COCs. In addition, exposure definitions in the publication are very broad and therefore imprecise: for each episode of use the time from the date of the first prescription until the end of the last prescription plus 45 days was used and for consecutive prescriptions, these were considered part of the same episode of use if the elapsed time between the end date of any one prescription and the issue of the next did not exceed 100 days. In addition, it is not clear to which exposure groups switchers were allocated.

In addition to the challenges of identifying true VTE cases from a database, with only partial clinical record review, the authors further restrict their study to “idiopathic cases”. The definition for “idiopathic VTE” varies across the literature, including between manuscripts from one of the lead authors (SS Jick) (Table 2). This introduces an additional source of bias in interpreting the data.

Similarly, a family history of VTE is a widely acknowledged risk factor for VTE; it appears that such a family history should exclude a patient from the idiopathic VTE category. However, information on a family history of VTE is not available within the GPRD database. This is viewed as a significant inconsistency.

It is also unclear as to how thoroughly a personal history of VTE was ruled-out. The authors state in the manuscript that women with previous VTE were excluded, but the history information might have been very limited because users could be included in the study if at least one year of recorded medical information before the index date was available. There is no further information on this issue in the publication to identify how much retrospective history information was available for the analysis and how many women had to be excluded due any potential prior episode of VTE by treatment group. While it is acknowledged by Bayer that it is unlikely that women with a prior history of VTE would have been started on a COC, in the context of UK clinical practice, this cannot be ruled-out and may be an additional source of bias.

Beyond the criteria used to exclude VTE cases from the “idiopathic” group (Table 2), the authors also excluded up front a number of individuals from the study cohort on the basis of underlying medical conditions (Table 3). Some of these conditions are widely acknowledged as risk factors for VTE (e.g., history of cancer), but many of the

other baseline exclusion criteria are not generally acknowledged as risk factors for VTE (e.g., autoimmune disorders). The authors do not provide a justification for excluding these patients. Since there is no information available about potential age differences between the LNG- and DRSP-COC cohorts and since the prevalence of many of the excluded conditions increases with increasing age, it is difficult to understand if these exclusion criteria have influenced the results of the study. At the very least, the authors should show how the exclusion criteria were applied in the two exposed groups (as discussed above).

The focus on “idiopathic” cases probably led to the exclusion of a majority of the VTE cases available for analysis in the study, unfortunately no details are presented in the publication, therefore the proportion of excluded cases remain unknown. An extrapolated analysis of overall VTE event rates cannot be conducted for this study.

3.3 Interpreting the current study from a clinical perspective and in the context of existing body of literature

As highlighted for the prior study in Section 2.3 above, elements of this study also make it very challenging to relate the findings to the existing body of literature, especially the focus on “idiopathic” cases, as has already been discussed in Section 2.3.

3.4 Bayer’s Overall Assessment of the Manuscript

Bayer’s assessment of this manuscript, based on the GPRD, is that the reliability of the findings and conclusions are seriously compromised. This is predominantly driven by the lack of an appropriate comparator for DRSP-COC within this study. Yasmin, the only DRSP-COC currently available in the UK, is extremely likely to be prescribed to a very different patient group, based on differing medical needs, than the widely used LNG-COCs. The lack of a thorough clinical record validation for cases, and other elements of the study methodology, may have further compromised the reliability of the data generated, yielding unexpected findings (e.g., higher number of PE cases compared to VTE, very low VTE event rates for LNG-COC users).

4. Bayer's Overall Conclusion

Bayer is committed to patient safety and ensuring that its COCs present a favorable benefit-risk profile, when used as directed. From the onset, Bayer was committed to monitoring and validating a positive benefit-risk profile for its DRSP-COCs. This commitment has been reflected in the conduct of the EURAS and LASS studies, the Ingenix study and the ongoing INAS-OC study. These efforts have been further expanded to other COCs (e.g., INAS-SCORE for Qlaira/Natazia, INAS-FOCUS for Beyaz/Safyral) and even to the study of VTE risk among post-menopausal women (EURAS-HRT for Angeliq). All of these studies have been undertaken in consultation with major Regulatory Authorities (EMA, FDA) and final study reports, publications or interim study reports for ongoing studies have been shared with Regulatory Authorities around the world.

Overall, Bayer's analysis of these two recently published manuscripts identifies significant concerns about the reliability of the findings and the conclusions presented by the authors. Specific source of these concerns have been presented in the current document. Given the already large, robust and consistent scientific body of evidence, it is Bayer's opinion that these two studies do not change the overall assessment about the benefit-risk profile of Bayer's DRSP-COCs.

Bayer re-affirms that, based on the best available scientific evidence, the risk of developing venous thromboembolism, or blood clots, in women using DRSP-COCs is comparable to other combination birth control pills studied, including those containing LNG.

5. References

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APPENDIX 1 – Bayer Commentary on the US PharMetrics Database

- The PharMetrics database contains data contributed by over 100 health plans. The database includes demographic information (such as patient's year of birth and sex), inpatient and outpatient claims, and diagnoses and procedures based on the ICD-9 (International Classification of Diseases, 9th revision) coding system and the CPT-4 (Current Procedural Terminology-4) system. It also contains retail and mail order prescription records which include the date dispensed, quantity dispensed, length of the supply, and the National Drug Code (NDC) for each drug claim¹.
- Some participating plans submit medical claims data only and do not include prescription data. When requesting data from PharMetrics, it is possible to request data only from those plans that submit both medical and pharmaceutical information.
- The database is useful for pharmacoeconomic studies because it contains information on cost of claims.
- Health plans submit only deidentified data to PharMetrics. An individual's continued presence in the database depends on a number of factors². For example:
 - If an individual patient remains with a single health plan, all medical information remains available under one identifier for as long as the patient remains with the same plan
 - If a patient changes to another health plan that communicates with the original health plan, all medical information continues to be available under the same identifier in the same way as above
 - If a patient changes to another health plan that does not communicate with the original health plan, the new plan assigns its own identifier and the patient essentially becomes a new subject in the database. In this way, a single patient who changes health plans can be represented in the database as two (or more) distinct individuals over the course of time. If the patient returns to a previous health plan, data from that point forward is captured under the previous identifier.
 - If a patient changes to another health plan that submits medical, but not pharmaceutical data to PharMetrics, and a data request requires pharmaceutical information, the patient will no longer be captured in the requested sample.
 - If a patient changes to another health plan that does not submit any information to PharMetrics, the patient will no longer be captured in the database so long as she participates with that plan. The patient may reenter the database in the future under a new, or a previous identifier, depending on the next health plan.
 - If a patient loses insurance coverage for greater than one month and then is reinstated to the same plan, the patient will have no information recorded

- in the database for the period of time without coverage, but then will reenter the database and continue under the same identifier.
- At any point, depending on the health plan, an individual can enter, leave, or reenter the database under one or multiple identifiers.
 - When a request is made for data, a report is provided showing the monthly eligibility for each identifier. Comparison of this report to the list of subjects is necessary in order to ensure that a subject was continuously eligible (i.e. had no missing months of data) for the entire study period. Most database studies note that subjects were “continuously eligible”. According to PharMetrics, longitudinal data has an average member enrollment period of two years.
 - Clinical information in PharMetrics is limited only to that which is submitted by the health care provider for insurance claim purposes at the time of patient encounter (through ICD-9 and CPT coding). Clinical data, such as vital signs or physical examination, do not exist in a claims database.
 - Most of the health plans submitting information to PharMetrics limit the number of diagnoses that can be submitted with each claim. PharMetrics itself limits the number of diagnosis codes per encounter to four. According to the rules for ICD-9 coding³, assigning a code is inappropriate for reporting purposes unless the health care provider (HCP) provides documentation to support the condition’s significance for the episode of care (e.g. a code for obesity can be used only if the HCP documents how obesity was addressed during the patient encounter).
 - “Personal history, family history, and genetic susceptibility to disease” are documented through the use of a supplemental classification of ICD-9 codes called “V-codes”. Except under very specific circumstances, these codes are not ordinarily assigned unless the history status or problem has some significance for the episode of care.
 - In the inpatient setting, when a diagnosis at the time of discharge is reported as “suspected”, “possible”, or “rule out”, the condition is coded and reported as though the diagnosis was established. These are ultimately the codes reported to PharMetrics. “Physicians are often unaware that official coding guidelines require a diagnosis qualified as unconfirmed to be coded as if established”³.

¹Information available on the PharMetrics website: www.imshealth.com/payersolutions

²Personal communication

³ICD-9-CM Coding Handbook 2011



10.3 Appendix 3: Approved US labeling

10.3.1 Yasmin

YASMIN 28 TABLETS **(drospirenone and ethinyl estradiol)**

PHYSICIAN LABELING

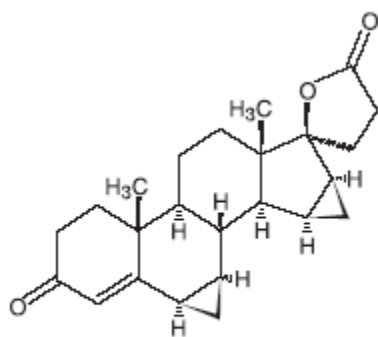
Rx only

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

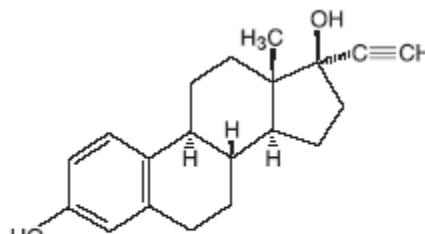
DESCRIPTION

YASMIN[®] provides an oral contraceptive regimen consisting of 21 active film coated tablets each containing 3 mg of drospirenone and 0.03 mg of ethinyl estradiol and 7 inert film coated tablets. The inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxypropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment, yellow NF. The inert film coated tablets contain lactose monohydrate NF, corn starch NF, povidone 25000 USP, magnesium stearate NF, hydroxypropylmethyl cellulose USP, talc USP, titanium dioxide USP.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa-6,7:15,16] cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of C₂₄H₃₀O₃. Ethinyl estradiol (19-nor-17 α -pregna 1,3,5(10)-triene-20-yne-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of C₂₀H₂₄O₂. The structural formulas are as follows:



Drospirenone



Ethinyl estradiol

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Combination oral contraceptives (COCs) act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

Drospirenone is a spironolactone analogue with antimineralocorticoid activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

PHARMACOKINETICS

Absorption

The absolute bioavailability of drospirenone (DRSP) from a single entity tablet is about 76%. The absolute bioavailability of ethinyl estradiol (EE) is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of **YASMIN** which is a combination tablet of drospirenone and ethinyl estradiol has not been evaluated. Serum concentrations of DRSP and EE reached peak levels within 1–3 hours after administration of **YASMIN**. After single dose administration of **YASMIN**, the relative bioavailability, compared to a suspension, was 107% and 117% for DRSP and EE, respectively.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1–10 mg. Following daily dosing of **YASMIN**, steady state DRSP concentrations were observed after 10 days. There was about 2 to 3 fold accumulation in serum C_{\max} and AUC (0–24h) values of DRSP following multiple dose administration of **YASMIN** (see TABLE I).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of **YASMIN** serum C_{\max} and AUC(0–24h) values of EE accumulate by a factor of about 1.5 to 2.

TABLE I TABLE OF MEAN PHARMACOKINETIC PARAMETERS OF YASMIN (Drospirenone 3 mg and Ethinyl Estradiol 0.03 mg)

Drospirenone Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{\max} (ng/mL)	T_{\max} (h)	AUC(0–24h) (ng•h/mL)	$t_{1/2}$ (h)
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA ^a
1/21	12	87.5 (59)	1.7 (20)	827 (23)	30.9 (44)
6/21	12	84.2 (19)	1.8 (19)	930 (19)	32.5 (38)
9/21	12	81.3 (19)	1.6 (38)	957 (23)	31.4 (39)
13/21	12	78.7 (18)	1.6 (26)	968 (24)	31.1 (36)

Ethinyl Estradiol Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{\max} (pg/mL)	T_{\max} (h)	AUC(0–24h) (pg•h/mL)	$t_{1/2}$ (h)
1/1	11	53.5 (43)	1.9 (45)	280.3 (87)	NA ^a
1/21	11	92.1 (35)	1.5 (40)	461.3 (94)	NA ^a
6/21	11	99.1 (45)	1.5 (47)	346.4 (74)	NA ^a
9/21	11	87 (43)	1.5 (42)	485.3 (92)	NA ^a
13/21	10	90.5 (45)	1.6 (38)	469.5 (83)	NA ^a

a) NA = Not available

Effect of Food

The rate of absorption of DRSP and EE following single administration of two YASMIN tablets was slower under fed conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast the extent of absorption of EE was reduced by about 20% under fed conditions.

Distribution

DRSP and EE serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4–5 L/kg.

DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Metabolism

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone- 3-sulfate. These metabolites were shown not to be pharmacologically active. In in vitro studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by cytochrome P450 3A4 (CYP3A4).

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver are responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38–47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17–20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Special Populations

Race

The effect of race on the disposition of **YASMIN** has not been evaluated.

Hepatic Dysfunction

YASMIN is contraindicated in patients with hepatic dysfunction (also see **BOLDED WARNINGS**). The mean exposure to DRSP in women with moderate liver impairment is approximately three times the exposure in women with normal liver function.

Renal Insufficiency

YASMIN is contraindicated in patients with renal insufficiency (also see **WARNINGS**).

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30–65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study 7 subjects continued the use of potassium sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CL_{Cr}, 50–80 mL/min) were comparable to those in the group with normal renal function (CL_{Cr}, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL_{Cr}, 30–50 mL/min) compared to those in the group with normal renal function. DRSP treatment was well tolerated by all groups. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs.

INDICATIONS AND USAGE

YASMIN is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

Oral contraceptives are highly effective. TABLE II lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE II Percentage of women experiencing an unintended pregnancy during the first year of typical use and first year of perfect use of contraception and the percentage continuing use at the end of the first year: United States.

Method (1)	% of Women Experiencing an Accidental Pregnancy Within the First Year of Use		% of Women Continuing Use At One Year ^a
	Typical Use ^b (2)	Perfect Use ^c (3)	(4)
Chance ^d	85 85		
Spermicides ^e	26 6		40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Sympto-thermal ^f	2		
Post-ovulation		1	
Withdrawal 19		4	
Cap ^g			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm ^g	20 6		56
Condom ^h			
Female (Reality)	21	5	56
Male 14		3	61
Pill 5			71
progestin only		0.5	
combined		0.1	
IUD			
Progesterone T:	2	1.5	81
Copper T 380A	0.8	0.6	78
Lng 20	0.1	0.1	81
Depo Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.1	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%ⁱ

Lactational Amenorrhea Method: LAM is highly effective, *temporary* method of contraception^j

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

- a) Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

- b) Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
- c) Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason.
- d) The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
- e) Foams, creams, gels, vaginal suppositories, and vaginal film.
- f) Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
- g) With spermicidal cream or jelly.
- h) Without spermicides.
- i) The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).
- j) However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches six months of age.

In clinical efficacy studies of **YASMIN** of up to 2 years duration, 2,629 subjects completed 33,160 cycles of use without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16 to 37 years. The racial demographic was: 83% Caucasian, 1% Hispanic, 1% Black, <1% Asian, <1% other, <1% missing data, 14% not inquired and <1% unspecified. Pregnancy rates in the clinical trials were less than one per 100 woman-years of use.

CONTRAINDICATIONS

YASMIN should not be used in women who have the following:

- Renal insufficiency
- Hepatic dysfunction
- Adrenal insufficiency
- Thrombophlebitis or thromboembolic disorders
- A past history of deep-vein thrombophlebitis or thromboembolic disorders
- Cerebral-vascular or coronary-artery disease
- Valvular heart disease with thrombogenic complications
- Severe hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding

- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Liver tumor (benign or malignant) or active liver disease
- Known or suspected pregnancy
- Heavy smoking (≥ 15 cigarettes per day) and over age 35

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

YASMIN contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. YASMIN should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium, should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiologic methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of

heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (Table III) among women who use oral contraceptives.

TABLE III. (Adapted from P.M. Layde and V. Beral) CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN-YEARS BY AGE SMOKING STATUS AND ORAL CONTRACEPTIVE USE				
AGE	EVER-USERS NON- SMOKERS	EVER-USERS SMOKERS	CONTROL NON- SMOKERS	CONTROL SMOKERS
15–24	0	10.5	0	0
25–34	4.4	14.2	2.7	4.2
35–44	21.5	63.4	6.4	15.2
45+	52.4	206.7	11.4	27.9

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see **section 9** in **WARNINGS**). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in the relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued from at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery.

Several studies have investigated the relative risks of thromboembolism in women using **YASMIN** compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of **YASMIN** approval.^{1, 2} The first (EURAS) showed the risk of

thromboembolism (particularly venous thromboembolism) and death in **YASMIN** users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in **YASMIN** users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed **YASMIN**.

Two additional epidemiological studies, one case-control study (van Hylckama Vlieg et al.³) and one retrospective cohort study (Lidegaard et al.⁴) suggested that the risk of venous thromboembolism occurring in **YASMIN** users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of **YASMIN** cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for **YASMIN** users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of **YASMIN** to that for users of other COC products.

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor, for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which provides satisfactory results in the individual.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women aged 40 to 49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table IV). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's — but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, women of all ages who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE IV
ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS
ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE
WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods ^a	7	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker ^b	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker ^b	2.2 3.4		6.6	13.5	51.1	117.2
IUD ^b	0.8	0.8	1	1	1.4	1.4
Condom ^a	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide ^a	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence ^a	2.5	1.6	1.6	1.7	2.9	3.6

a) Deaths are birth-related

b) Deaths are method-related

Adapted from H.W. Ory, Family Planning Perspectives, 15:57-63, 1983.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of COCs. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. The risk does not appear to increase with duration of use and no consistent relationships have been found with dose or type of steroid. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history. Some studies have found a small increase in risk for women who first use COCs before age 20.

Breast cancers diagnosed in current or previous OC users tend to be less clinically advanced than in nonusers.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormonally-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years

of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed dosing schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS, 1a** and **1d**), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

1. GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

2. PHYSICAL EXAMINATION AND FOLLOW-UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

3. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

4. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

5. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

6. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

7. CONTACT LENSES

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

8. DRUG INTERACTIONS

Effects of Other Drugs on Combined Hormonal Contraceptives

Rifampin

Metabolism of ethinyl estradiol and some progestins (e.g., norethindrone) is increased by rifampin. A reduction in contraceptive effectiveness and an increase in menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants

Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine have been shown to increase the metabolism of ethinyl estradiol and/or some progestins, which could result in a reduction of contraceptive effectiveness.

Antibiotics

Pregnancy while taking combined hormonal contraceptives has been reported when the combined hormonal contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effects of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin

Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively.

St. John's Wort

Herbal products containing St. John's Wort (*hypericum perforatum*) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of oral contraceptives and emergency contraceptive pills. This may also result in breakthrough bleeding.

Other

Ascorbic acid and acetaminophen may increase plasma concentrations of some synthetic estrogens, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and an increased incidence of menstrual irregularities has been suggested with phenylbutazone.

Effects of Drospirenone on Other Drugs

Metabolic Interactions

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies (see **Metabolism**). In *in vitro* studies DRSP

did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme.

The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose). Based on the available results of *in vivo* and *in vitro* studies it can be concluded that, at clinical dose level, DRSP shows little propensity to interact to a significant extent with cytochrome P450 enzymes.

Interactions With Drugs That Have The Potential To Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking **YASMIN** with other drugs (see **BOLDED WARNINGS**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the **YASMIN** clinical trials.

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.01 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations > 5.5 mEq/L).

Effects of Combined Hormonal Contraceptives on Other Drugs

Combined oral contraceptives containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance on temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

9. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine- and liver-function tests and blood components may be affected by oral contraceptives:

- a. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- b. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
- c. Other binding proteins may be elevated in serum.
- d. Sex-hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
- e. Triglycerides may be increased.
- f. Glucose tolerance may be decreased.

- g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

10. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1 to 2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. See **WARNINGS**.

11. PREGNANCY

Pregnancy category X. See **CONTRAINDICATIONS** and **WARNINGS**.

Estrogens and progestins should not be used during pregnancy. Fourteen pregnancies that occurred with **YASMIN** exposure *in utero* (none with more than a single cycle of exposure) have been identified. One infant was born with esophageal atresia. A causal association with **YASMIN** is unknown.

A teratology study in pregnant rats given drospirenone orally at doses of 5, 15 and 45 mg/kg/day, 6 to 50 times the human exposure based on AUC of drospirenone, resulted in an increased number of fetuses with delayed ossification of bones of the feet in the two higher doses. A similar study in rabbits dosed orally with 1, 30 and 100 mg/kg/day drospirenone, 2 to 27 times the human exposure, resulted in an increase in fetal loss and retardation of fetal development (delayed ossification of small bones, multiple fusions of ribs) at the high dose only. When drospirenone was administered with ethinyl estradiol (100:1) during late pregnancy (the period of genital development) at doses of 5, 15 and 45 mg/kg, there was a dose dependent increase in feminization of male rat fetuses. In a study in 36 cynomolgous monkeys, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinyl estradiol (100:1) at doses up to 10 mg/kg/day drospirenone, 30 times the human exposure.

12. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

After oral administration of **YASMIN** about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant.

13. PEDIATRIC USAGE

Safety and efficacy of **YASMIN** have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

INFORMATION FOR THE PATIENT

See Patient Labeling printed below.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS**).

- Thrombophlebitis
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

- Mesenteric thrombosis
- Retinal thrombosis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum

- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and a causal association has been neither confirmed nor refuted:

- Acne
- Budd-Chiari syndrome
- Cataracts
- Changes in appetite
- Changes in libido
- Colitis
- Cystitis-like syndrome
- Dizziness
- Erythema multiforme
- Erythema nodosum
- Headache
- Hemolytic uremic syndrome
- Hemorrhagic eruption
- Hirsutism
- Impaired renal function
- Loss of scalp hair
- Nervousness
- Porphyria
- Pre-menstrual syndrome
- Vaginitis

The following are the most common adverse events reported with use of **YASMIN** during the clinical trials, occurring in > 1% of subjects and which may or may not be drug related: Headache, Menstrual Disorder, Breast Pain, Abdominal Pain, Nausea, Leukorrhea, Flu Syndrome, Acne, Vaginal Moniliasis, Depression, Diarrhea, Asthenia, Dysmenorrhea, Back Pain, Infection, Pharyngitis, Intermenstrual Bleeding, Migraine, Vomiting, Dizziness, Nervousness, Vaginitis, Sinusitis, Cystitis, Bronchitis, Gastroenteritis, Allergic Reaction, Urinary Tract Infection, Pruritus, Emotional Lability, Surgery, Rash, Upper Respiratory Infection.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of other oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females. Drospirenone, however, is a spironolactone analogue which has

antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.

Effects on menses

- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron-deficiency anemia
- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation

- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

Effects from long-term use

- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease
- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer

DOSAGE AND ADMINISTRATION

YASMIN

To achieve maximum contraceptive effectiveness, **YASMIN** (drospirenone and ethinyl estradiol) must be taken exactly as directed at intervals not exceeding 24 hours.

YASMIN consists of 21 tablets of a monophasic combined hormonal preparation plus 7 inert tablets. The dosage of **YASMIN** is one yellow tablet daily for 21 consecutive days followed by 7 white inert tablets per menstrual cycle. A patient should begin to take **YASMIN** either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start. During the first cycle of **YASMIN** use, the patient should be instructed to take one yellow **YASMIN** daily, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) She should take one yellow **YASMIN** daily for 21 consecutive days, followed by one white inert tablet daily on menstrual cycle days 22 through 28. It is recommended that **YASMIN** be taken at the same time each day, preferably after the evening meal or at bedtime. If **YASMIN** is first taken later than the first day of the menstrual cycle, **YASMIN** should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start. During the first cycle of **YASMIN** use, the patient should be instructed to take one yellow **YASMIN** daily, beginning on the first Sunday after the onset of her menstrual period. She should take one yellow **YASMIN** daily for 21 consecutive days, followed by one white inert tablet daily on menstrual cycle days 22 through 28. It is recommended that **YASMIN** be taken at the same time each day, preferably after the evening meal or at bedtime. **YASMIN** should not be considered effective as a contraceptive until after the first 7 consecutive days of product

administration. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of **YASMIN** on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her yellow tablets on the next day after ingestion of the last white tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of **YASMIN** is started later than the day following administration of the last white tablet, the patient should use another method of contraception until she has taken a yellow **YASMIN** daily for seven consecutive days.

When switching from another oral contraceptive, **YASMIN** should be started on the same day that a new pack of the previous oral contraceptive would have been started.

Withdrawal bleeding usually occurs within 3 days following the last yellow tablet. If spotting or breakthrough bleeding occurs while taking **YASMIN**, the patient should be instructed to continue taking her **YASMIN** as instructed and by the regimen described above. She should be instructed that this type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient should be advised to consult her physician.

Although the occurrence of pregnancy is unlikely if **YASMIN** is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), the possibility of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. Hormonal contraception should be discontinued if pregnancy is confirmed.

The risk of pregnancy increases with each active yellow tablet missed. For additional patient instructions regarding missed pills, see the "WHAT TO DO IF YOU MISS PILLS" section in the DETAILED PATIENT LABELING which follows. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more white tablets, she should still be protected against pregnancy provided she begins taking yellow tablets again on the proper day.

In the nonlactating mother, **YASMIN** may be initiated 4 weeks postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** concerning thromboembolic disease.)

HOW SUPPLIED

YASMIN 28 Tablets (drospirenone and ethinyl estradiol) are available in packages of 3 BLISTER packs (NDC 50419-402-03).

Each pack contains 21 active yellow round, unscored, film coated tablets each containing 3 mg drospirenone and 0.03 mg ethinyl estradiol, and 7 inert white round, unscored, film coated tablets.

Store at 25° C (77°F); excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.]

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Manufactured for: Bayer HealthCare Pharmaceuticals Inc.

Manufactured in: Germany

BRIEF SUMMARY PATIENT PACKAGE INSERT

YASMIN[®] 28 Tablets

(drospirenone and ethinyl estradiol)

28 tablets containing the following:

21 yellow – "active" tablets

7 white – "inert" tablets

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

YASMIN is different from other birth-control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, you should not take YASMIN if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether YASMIN is right for you, and during the first month that you take YASMIN, you should have a blood test to check your potassium level.

- **NSAIDs (ibuprofen [Motrin[®], Advil[®]], naproxen [Naprosyn[®], Aleve[®] and others] when taken long-term and for treatment of arthritis or other problems)**
- **Potassium-sparing diuretics (spironolactone and others)**
- **Potassium supplementation**
- **ACE inhibitors (Capoten[®], Vasotec[®], Zestril[®] and others)**
- **Angiotensin-II receptor antagonists (Cozaar[®], Diovan[®], Avapro[®] and others)**
- **Heparin**

Oral contraceptives, also known as "birth-control pills" or "the pill," are taken to prevent pregnancy, and when taken correctly, have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 5% per year when women who miss pills are included. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, or malignant or benign liver tumors.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), blockage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.
4. Cancer of the breast. Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of getting breast cancer begin to go back down. You should have regular breast examinations by a healthcare provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants, some antibiotics and some herbal products such as St. John's Wort, may decrease oral contraceptive effectiveness.

Taking the pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is appropriate to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information booklet gives you further information which you should read and discuss with your healthcare provider.

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

INSTRUCTIONS TO PATIENTS

HOW TO TAKE THE PILL

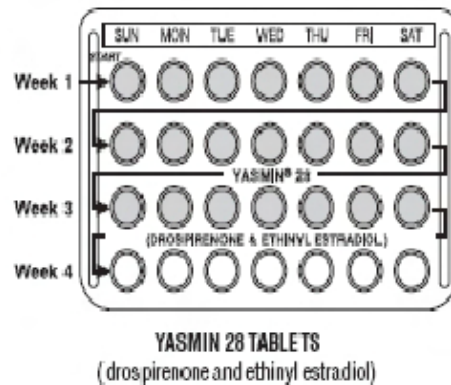
IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS

1. **BE SURE TO READ THESE DIRECTIONS:**
Before you start taking your pills. Anytime you are not sure what to do.
2. **THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.**
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1–3 PACKS OF PILLS.**
If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or healthcare provider.
4. **MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.**
On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. **IF YOU HAVE VOMITING OR DIARRHEA, or IF YOU TAKE SOME MEDICINES, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.**
Use a back-up method (such as condoms or spermicides) until you check with your doctor or healthcare provider.
6. **IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or healthcare provider about how to make pill-taking easier or about using another method of birth control.**
7. **IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or healthcare provider.**

BEFORE YOU START TAKING YOUR PILLS

1. **DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.**
It is important to take it at about the same time every day.
2. **LOOK AT YOUR PILL PACK - IT HAS 28 PILLS:**
The YASMIN pill pack has 21 yellow "active" pills (with hormones) to be taken for three weeks, followed by 7 white "reminder" pills (without hormones) to be taken for one week.
3. **ALSO FIND:**
 - 1) where on the pack to start taking pills,
 - 2) in what order to take the pills (follow the arrows)
 - 3) the week numbers as shown in the diagram below



4. **BE SURE YOU HAVE READY AT ALL TIMES:**
ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicides) to use as a back-up in case you miss pills.
AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. Decide with your doctor or healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first yellow "active" pill of the first pack during the *first 24 hours of your period*.
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first yellow "active" pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* (such as condoms or spermicides) as a back-up method if you have sex any time from the Sunday you start your first pack until the next Sunday (7 days).

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY**

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**

Start the next pack on the day after your last white "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** yellow "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** yellow "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. You **MAY BECOME PREGNANT** if you have sex in the *7 days* after you miss pills. You **MUST** use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you **MISS 2** yellow "active" pills in a row in the **3RD WEEK**:

1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking one pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or healthcare provider because you might be pregnant.
3. You **MAY BECOME PREGNANT** if you have sex in the *7 days* after you miss pills. You **MUST** use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you **MISS 3 OR MORE** yellow "active" pills in a row (during the first 3 weeks).

1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or healthcare provider because you might be pregnant.
3. You **MAY BECOME PREGNANT** if you have sex in the *7 days* after you miss pills. You **MUST** use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you forget any of the 7 white "reminder" pills in Week 4:

THROW AWAY the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD (such as condoms or spermicides) anytime you have sex.

KEEP TAKING ONE ACTIVE PILL EACH DAY until you can reach your doctor or healthcare provider.

For additional information see Detailed Patient Labeling

DETAILED PATIENT PACKAGE INSERT

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

YASMIN is different from other birth-control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, you should not take YASMIN if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether YASMIN is right for you, and during the first month that you take YASMIN, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin[®], Advil[®]], naproxen [Naprosyn[®], Aleve[®] and others] when taken long-term and for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten[®], Vasotec[®], Zestril[®] and others)
- Angiotensin-II receptor antagonists (Cozaar[®], Diovan[®], Avapro[®] and others)
- Heparin

INTRODUCTION

Any woman who considers using oral contraceptives (the birth-control pill or "the pill") should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this leaflet with him or her, both when you first start taking the pill and during your revisits. You should also follow your healthcare provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (one pregnancy per 100 women per year of use)

when used perfectly, without missing any pills. Typical failure rates, including women who don't always follow the instructions exactly, are about 5% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other nonsurgical methods of birth control during the first year of use are as follows:

Percentage of women experiencing an unintended pregnancy during the first year of typical use and first year of perfect use of contraception and the percentage continuing use at the end of the first year: United States.

Method (1)	% of Women Experiencing an Accidental Pregnancy Within the First Year of Use		% of Women Continuing Use At One Year ^a
	Typical Use ^b (2)	Perfect Use ^c (3)	(4)
Chance ^d	85 85		
Spermicides ^e	26 6		40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Sympto-thermal ^f	2		
Post-ovulation		1	
Withdrawal ¹⁹		4	
Cap ^g			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm ^g	20 6		56
Condom ^h			
Female (Reality)	21	5	56
Male 14		3	61
Pill 5			71
progestin only		0.5	
combined		0.1	
IUD			
Progesterone T:	2	1.5	81
Copper T 380A	0.8	0.6	78
Lng 20	0.1	0.1	81
Depo Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.1	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%ⁱ

Lactational Amenorrhea Method: LAM is highly effective, *temporary* method of contraception^j

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

- a) Among *typical* couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.
- b) Among couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
- c) Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason.
- d) The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
- e) Foams, creams, gels, vaginal suppositories, and vaginal film.
- f) Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
- g) With spermicidal cream or jelly.
- h) Without spermicides.
- i) The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).
- j) However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches six months of age.

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use YASMIN should not smoke.

Some women should not use the pill. For example, you should not take **YASMIN** if you are pregnant or think you may be pregnant. You should also not use **YASMIN** if you have had any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), brain (stroke) or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)

- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

In addition, you should not use YASMIN if you have any of the following conditions:

- Kidney Disease
- Liver Disease
- Adrenal Disease

Tell your healthcare provider if you have ever had any of the above conditions (Your healthcare provider can recommend another method of birth control). If you are currently on daily, long-term treatment for a chronic condition with any of the following medications, you should consult your healthcare provider before taking **YASMIN**:

- NSAIDs (ibuprofen, naproxen and others)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (captopril, enalapril, lisinopril and others)
- Angiotensin-II receptor antagonists (Cozaar[®], Diovan[®], Avapro[®] and others)
- Heparin

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your healthcare provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or healthcare provider if you smoke or take any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. RISK OF DEVELOPING BLOOD CLOTS

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives and can be fatal. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives three to four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby or a mid-trimester pregnancy loss or termination. It is advisable to wait for at least four weeks after delivery if you are not breast-feeding. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on breast-feeding in **GENERAL PRECAUTIONS**.)

2. HEART ATTACKS AND STROKES

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. GALLBLADDER DISEASE

Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. LIVER TUMORS

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in two studies, in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

5. CANCER OF THE REPRODUCTIVE ORGANS AND BREASTS

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of getting breast cancer begin to go back down. You should have regular breast examinations by a healthcare provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

**ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS
ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE
WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE**

Method of Control and Outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods ^a	7	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker ^b	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker ^b	2.2	3.4	6.6	13.5	51.1	117.2
IUD ^b	0.8	0.8	1	1	1.4	1.4
Condom ^a	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide ^a	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence ^a	2.5	1.6	1.6	1.7	2.9	3.6

a) Deaths are birth-related

b) Deaths are method-related

Adapted from H.W. Ory, Family Planning Perspectives, 15:57-63, 1983.

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7–26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, except for those women over the age of 40, when the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older high-dose pills and on less-selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest-dose pill that is effective.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)

- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or healthcare provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. VAGINAL BLEEDING

Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or healthcare provider.

2. CONTACT LENSES

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or healthcare provider.

3. FLUID RETENTION

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or healthcare provider.

4. MELASMA

A spotty darkening of the skin is possible, particularly of the face.

5. OTHER SIDE EFFECTS

Other side effects may include nausea, vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects occur, call your doctor or healthcare provider.

GENERAL PRECAUTIONS

1. Missed periods and use of oral contraceptives before or during early pregnancy.

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your healthcare provider immediately to determine whether you are pregnant. Stop taking oral contraceptives if pregnancy is confirmed.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these studies have not been confirmed. Nevertheless, oral contraceptives should not be used during pregnancy. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While Breast-Feeding

If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant, and this partial protection decreases significantly as you breast-feed for longer periods of time. You should consider starting oral contraceptives only after you have weaned your child completely.

3. Laboratory Tests

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

4. Drug Interactions

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. Herbal products containing St. John's Wort (*hypericum perforatum*) may reduce the effectiveness of oral contraceptives. This may also result in breakthrough bleeding. You may need to use an additional method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective (**also See BOLDDED TEXT AT BEGINNING**).

5. Sexually Transmitted Diseases

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER BEFORE YOU START TAKING YOUR PILLS

1. **BE SURE TO READ THESE DIRECTIONS:**
Before you start taking your pills.
Any time you are not sure what to do.
2. **THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.**
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1–3 PACKS OF PILLS.**
If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the

pill. The problem will usually go away. If it does not go away, check with your doctor or healthcare provider.

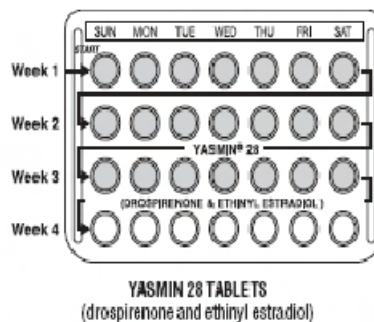
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.
Use a back-up method (such as condoms or spermicides) until you check with your doctor or healthcare provider.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or healthcare provider about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or healthcare provider.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK - IT HAS 28 PILLS: The YASMIN pill pack has 21 yellow "active" pills (with hormones) to be taken for three weeks, followed by 7 white "reminder" pills (without hormones) to be taken for one week.
3. ALSO FIND:
 - 1) where on the pack to start taking pills,
 - 2) in what order to take the pills (follow the arrows)
 - 3) the week numbers as shown in the diagram below



4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicides) to use as a back-up in case you miss pills.
AN EXTRA, FULL PILL PACK.

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. Decide with your doctor or healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first yellow "active" pill of the first pack during the *first 24 hours of your period*.
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first yellow "active" pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* (such as condoms or spermicides) as a back-up method if you have sex any time from the Sunday you start your first pack until the next Sunday (7 days).

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY** Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
2. Do not skip pills even if you do not have sex very often.
3. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:** Start the next pack on the day after your last white "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** yellow "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** yellow "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. You **MAY BECOME PREGNANT** if you have sex in the *7 days* after you miss pills. You **MUST** use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you **MISS 2** yellow "active" pills in a row in the **3RD WEEK:**

1. **If you are a Day 1 Starter:**
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking one pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or healthcare provider because you might be pregnant.
3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you **MISS 3 OR MORE** yellow "active" pills in a row (during the first 3 weeks).

1. **If you are a Day 1 Starter:**

THROW OUT the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:

Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or healthcare provider because you might be pregnant.

You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you forget any of the 7 white "reminder" pills in Week 4:

THROW AWAY the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD (such as condoms or spermicides) any time you have sex.

KEEP TAKING ONE ACTIVE PILL EACH DAY until you can reach your doctor or healthcare provider.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately less than 1% (one pregnancy per 100 women per year of use) if taken every day as directed, but more typical failure rates are about 5%. If failure does occur with **YASMIN** use, the risk to the fetus is unknown.

PREGNANCY AFTER STOPPING THE PILL

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE

Serious ill effects have not been reported following ingestion of large doses of other oral contraceptives by young children. Overdosage of **YASMIN** may cause nausea and withdrawal bleeding in females and may increase blood levels of potassium or decrease blood levels of sodium, which could be dangerous. In case of overdosage, contact your healthcare provider.

OTHER INFORMATION

Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is appropriate to postpone it. You should be re-examined at least once a year. Be sure to inform your healthcare provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments

with your healthcare provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ovarian cysts may occur less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus

If you want more information about birth-control pills, ask your doctor or pharmacist. They have a more technical leaflet called the Prescribing Information which you may wish to read.

Manufactured by

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Manufactured in Germany

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10.3.2 Safyral

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SAFYRAL safely and effectively. See full prescribing information for SAFYRAL.

SAFYRAL (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)

Initial U.S. Approval: 2010

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning

- Women over 35 years old who smoke should not use Safyral. (4)
- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)

INDICATIONS AND USAGE

Safyral is an estrogen/progestin COC containing a folate, indicated for use by women to:

- prevent pregnancy. (1.1)
- raise folate levels in women who choose to use an oral contraceptive for contraception. (1.2)

DOSAGE AND ADMINISTRATION

- Take one tablet daily by mouth at the same time every day. (2.1)
- Tablets must be taken in the order directed on the blister pack. (2.1)

DOSAGE FORMS AND STRENGTHS

Safyral consists of 28 film-coated, biconvex tablets in the following order (3):

- 21 orange tablets, each containing 3 mg drospirenone (DRSP), 0.03 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium,
- 7 light orange tablets, each containing 0.451 mg levomefolate calcium

CONTRAINDICATIONS

- Renal impairment or adrenal insufficiency (4)
- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

WARNINGS AND PRECAUTIONS

- Vascular risks: Stop Safyral if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Hyperkalemia: DRSP has antimineralocorticoid activity. Do not use in patients predisposed to hyperkalemia. Check serum potassium level during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium. (5.2, 7.3)
- Liver disease: Discontinue Safyral if jaundice occurs. (5.4)
- High blood pressure: Do not prescribe Safyral for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Safyral. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- Headache: Evaluate significant change in headaches and discontinue Safyral if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

ADVERSE REACTIONS

The most frequent (> 2 %) adverse reactions in contraception and folate clinical trials are as follows: premenstrual syndrome (12.4%), headache /migraine (10.3%), breast pain/tenderness/discomfort (8.1%), nausea/vomiting (4.4%), abdominal pain/tenderness/discomfort (2.2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes (e.g., CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

1 INDICATIONS AND USAGE

- 1.1 Oral Contraceptive
- 1.2 Folate Supplementation

2 DOSAGE AND ADMINISTRATION

- 2.1 How to Take Safyral
- 2.2 How to Start Safyral
- 2.3 Advice in Case of Gastrointestinal Disturbances
- 2.4 Folate Supplementation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Thromboembolic Disorders and Other Vascular Problems
- 5.2 Hyperkalemia
- 5.3 Carcinoma of the Breasts and Reproductive Organs
- 5.4 Liver Disease
- 5.5 High Blood Pressure
- 5.6 Gallbladder Disease
- 5.7 Carbohydrate and Lipid Metabolic Effects
- 5.8 Headache
- 5.9 Bleeding Irregularities
- 5.10 COC Use Before or During Early Pregnancy
- 5.11 Depression
- 5.12 Interference with Laboratory Tests
- 5.13 Monitoring
- 5.14 Other Conditions

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Other Drugs on Combined Hormonal Contraceptives
- 7.2 Effects of Combined Oral Contraceptives on Other Drugs
- 7.3 Interactions that Have the Potential to Increase Serum Potassium
- 7.4 Effects of Folates on Other Drugs
- 7.5 Effects of Other Drugs on Folates

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Renal Impairment
- 8.7 Patients with Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Oral Contraceptive Clinical Trial
- 14.2 Folate Supplementation Clinical Trials

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage Conditions

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. [See Contraindications (4)].

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Safyral is indicated for use by women to prevent pregnancy.

1.2 Folate Supplementation

Safyral is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Safyral

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

To achieve maximum contraceptive effectiveness, Safyral must be taken as directed. Single missed pills should be taken as soon as remembered.

2.2 How to Start Safyral

Instruct the patient to begin taking Safyral either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start

During the first cycle of Safyral use, instruct the patient to take one orange Safyral daily, beginning on Day one (1) of her menstrual cycle. (The first day of menstruation is Day one.) She should take one orange Safyral daily for 21 consecutive days, followed by one light orange tablet, containing levomefolate alone, daily on days 22 through 28. Safyral should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Safyral can be taken without regard to meals. If Safyral is first taken later than the first day of the menstrual cycle, Safyral should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start

During the first cycle of Safyral use, instruct the patient to take one orange Safyral daily, beginning on the first Sunday after the onset of her menstrual period. She should take one orange Safyral daily for 21 consecutive days, followed by one light orange tablet, containing levomefolate alone, daily on days 22 through 28. Safyral should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Safyral can be taken without regard to meals. Safyral should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Safyral on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her orange tablets on the next day after ingestion of the last light orange folate tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Safyral is started later than the day following administration of the last light

orange tablet, the patient should use another method of contraception until she has taken an orange Safyral daily for seven consecutive days.

When switching from a different birth control pill

When switching from another birth control pill, Safyral should be started on the same day that a new pack of the previous oral contraceptive would have been started.

When switching from a method other than a birth control pill

When switching from a transdermal patch or vaginal ring, Safyral should be started when the next application would have been due. When switching from an injection, Safyral should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Safyral should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last orange tablet. If spotting or breakthrough bleeding occurs while taking Safyral, the patient should be instructed to continue taking her Safyral by the regimen described above. Counsel her that this type of bleeding is usually transient and without significance; however, advise her that if the bleeding is persistent or prolonged, she should consult her healthcare provider.

Although the occurrence of pregnancy is low if Safyral is taken according to directions, if withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Safyral if pregnancy is confirmed.

The risk of pregnancy increases with each active orange tablet missed. For additional patient instructions regarding missed pills, see the **“WHAT TO DO IF YOU MISS PILLS”** section in the **FDA-Approved Patient Labeling** which follows. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more light orange tablets, she should still be protected against pregnancy provided she begins taking a new cycle of orange tablets on the proper day.

For postpartum women who do not breastfeed or after a second trimester abortion, start Safyral no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts Safyral postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Safyral for 7 consecutive days.

2.3 Advice in case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, this can be regarded as a missed tablet.

2.4 Folate Supplementation

The U.S. Preventive Services Task Force recommends that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily.¹ Consider other folate supplementation that a woman may be taking before prescribing Safyral. Ensure that folate supplementation is maintained if a woman discontinues Safyral due to pregnancy.

3 DOSAGE FORMS AND STRENGTHS

Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is available in blister packs.

Each blister pack contains 28 film-coated, round, bi-convex tablets in the following order:

- 21 orange tablets each containing 3 mg drospirenone (DRSP), 0.03 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium embossed with a “Y+” in a regular hexagon on one side.
- 7 light orange tablets each containing 0.451 mg levomefolate calcium embossed with a “M+” in a regular hexagon on one side

4 CONTRAINDICATIONS

Do not prescribe Safyral to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35 [*see Boxed Warning and Warnings and Precautions (5.1)*]
 - Have deep vein thrombosis or pulmonary embolism, now or in the past [*see Warnings and Precautions (5.1)*]
 - Have cerebrovascular disease [*see Warnings and Precautions (5.1)*]
 - Have coronary artery disease [*see Warnings and Precautions (5.1)*]
 - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [*see Warnings and Precautions (5.1)*]
 - Have inherited or acquired hypercoagulopathies [*see Warnings and Precautions (5.1)*]
 - Have uncontrolled hypertension [*see Warnings and Precautions (5.5)*]
 - Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.7)*]
 - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [*see Warnings and Precautions (5.8)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.9)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.3)*]
- Liver tumor (benign or malignant) or liver disease [*see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Safyral if an arterial or deep venous thrombotic (VTE) event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Safyral at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Safyral no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Safyral if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

Epidemiologic studies including a DRSP-containing COC

Several studies have investigated the relative risks of thromboembolism in women using a different DRSP-containing COC (Yasmin, which contains 0.03 mg of EE and 3 mg of DRSP) compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.^{2,3} The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive

preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.

Two additional epidemiological studies, one case-control study (van Hylckama Vlieg et al. ⁴) and one retrospective cohort study (Lidegaard et al. ⁵) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

5.2 Hyperkalemia

Safyral contains 3 mg of the progestin DRSP, which has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Safyral should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal impairment, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Safyral because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Safyral if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Safyral if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Safyral. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Safyral develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Safyral if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Data from ten Yasmin contraceptive efficacy clinical trials (N=2,467) show that the percent of women who took Yasmin and experienced unscheduled bleeding decreased over time from 12% at cycle 2 to 6% (cycle 13). A total of 25 subjects out of 3,009 in the Yasmin and Safyral trials (<1%) discontinued due to bleeding complaints. These are described as metrorrhagia, vaginal hemorrhage, menorrhagia, abnormal withdrawal bleeding, and menometrorrhagia.

The average duration of scheduled bleeding episodes in the majority of subjects (86%-88%) was 4-7 days. Women who use Safyral may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from Yasmin contraceptive efficacy trials, during cycles 2 –13, 1 - 11% of women per cycle experienced no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect when COCs are taken inadvertently during early pregnancy, particularly in so far as cardiac anomalies and limb-reduction defects are concerned. Discontinue Safyral if pregnancy is confirmed and initiate a prenatal vitamin containing folate supplementation.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

5.11 Depression

Women with a history of depression should be carefully observed and Safyral discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

Folates may mask vitamin B12 deficiency.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.4)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Contraception and Folate Supplementation Clinical Trials

The data provided reflect the experience with the use of Yasmin (3 mg DRSP/0.03 mg EE) in the adequate and well-controlled studies for contraception (N=2,837) and folate supplementation (N=172). For contraception, the US pivotal clinical study (N=326) for the oral contraception indication for Yasmin was a multicenter, open-label trial in healthy women aged 18 -35 who were treated with Yasmin for up to 13 cycles. The second contraceptive pivotal study was a multicenter, randomized, open-label comparative European study of Yasmin vs. 0.150 mg desogestrel/0.03 mg EE conducted in healthy women aged 17-40 who were treated for up to 26 cycles. The primary efficacy study using Safyral for folate supplementation was a randomized, single-center European trial in 172 healthy, female subjects aged 18 -40 years comparing the pharmacodynamic effects of Yasmin + 0.451 mg levomefolate calcium to Yasmin co-administered with folic acid during 24 weeks of treatment followed by 20 weeks of open-label Yasmin.

The adverse reactions seen across the 2 indications overlapped and are reported using the frequencies from the pooled dataset. The most common treatment-emergent adverse reactions ($\geq 2\%$ of users) were: premenstrual syndrome (12.4%), headache/migraine (10.3%), breast pain/tenderness/discomfort (8.1%), nausea/vomiting (4.4%) and abdominal pain/discomfort/tenderness (2.2%).

Adverse Reactions ($\geq 1\%$) Leading to Study Discontinuation:

Contraception Clinical Trials

Of 2,837 women, 6.7% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was headache/migraine (1.5%).

Folate Clinical Trial

There were no subjects who discontinued due to an adverse reaction.

Serious Adverse Reactions (Definitely, Probably, or Possibly Related to Study Drug):

Contraception Clinical Trials: depression, pulmonary embolism, toxic skin eruption, and uterine leiomyoma.

Folate Supplementation Clinical Trial: none reported in the clinical trial

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Yasmin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions, including fatalities, are grouped into System Organ Classes and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, intracardiac thrombosis, intracranial venous sinus thrombosis, sagittal sinus thrombosis, retinal vein occlusion, myocardial infarction and stroke), hypertension

Hepatobiliary disorders: Gallbladder disease

Immune system disorders: Hypersensitivity

Metabolism and nutrition disorders: Hyperkalemia

Skin and subcutaneous tissue disorders: Chloasma

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin with certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP450 enzymes at clinically relevant concentrations [see *Clinical Pharmacology* (12.3)].

7.3 Interactions that Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Safyral with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

7.4 Effects of Folates on Other Drugs

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

7.5 Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate levels by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE tablets (Yasmin), about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

Studies to date indicate there is no adverse effect of folate on nursing infants.

8.4 Pediatric Use

Safety and efficacy of Safyral has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Safyral has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Safyral is contraindicated in patients with renal impairment [see *Contraindications* (4) and *Warnings and Precautions* (5.2)].

Following administration of DRSP 3 mg daily for 14 days, the serum DRSP levels in subjects with mild renal impairment (creatinine clearance CL_{Cr}, 50-80 mL/min) were comparable to those in subjects with normal renal function (CL_{Cr}, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL_{Cr}, 30-50 mL/min) compared to those in the group with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment

whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs [see Clinical Pharmacology (12.3)].

8.7 Patients with Hepatic Impairment

Safyral is contraindicated in patients with hepatic disease [see *Contraindications (4) and Warnings and Precautions (5.4)*]. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Safyral has not been studied in women with severe hepatic impairment.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP however, is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Levomefolate calcium doses of 17 mg/day (37-fold higher than the levomefolate calcium dose of Safyral) were well tolerated after long-term treatment up to 12 weeks.

11 DESCRIPTION

Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) provides an oral contraceptive regimen consisting of 28 film-coated tablets that contain the active ingredients specified for each tablet below:

- 21 orange tablets each containing 3 mg DRSP, 0.03 mg EE as betadex clathrate, and 0.451 mg levomefolate calcium
- 7 light orange tablets each containing 0.451 mg levomefolate calcium

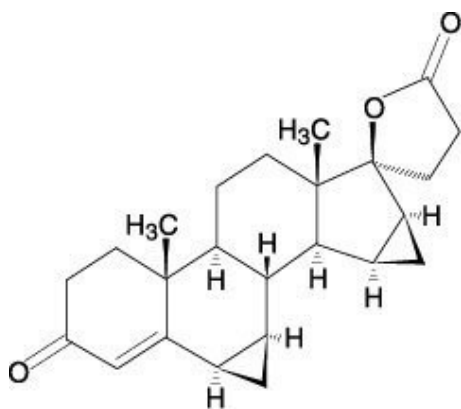
The inactive ingredients in the orange tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose USP, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF, ferric oxide pigment, yellow NF, and ferric oxide pigment, red NF. The light orange film-coated tablets contain 0.451 mg of levomefolate calcium. The inactive ingredients in the light orange tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose NF, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF and ferric oxide pigment, yellow NF, and ferric oxide pigment, red NF.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13, 14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa-6,7:15,16] cyclo-penta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$.

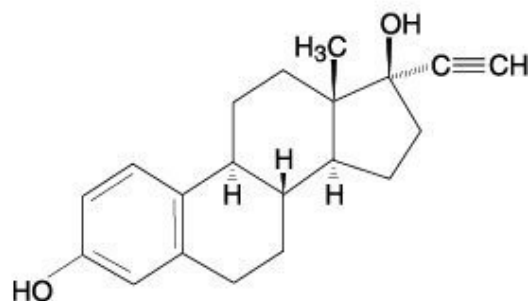
Ethinyl estradiol (19-nor-17 α -pregna 1,3,5(10)-triene-20-yne-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

Levomefolate calcium (N-[4-[[[2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridinyl)methyl]amino]benzoyl]-L-glutamic acid, calcium salt) is a synthetic calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF), which is a metabolite of vitamin B₉ and has a molecular weight of 497.5 and a molecular formula of $C_{20}H_{23}CaN_7O_6$.

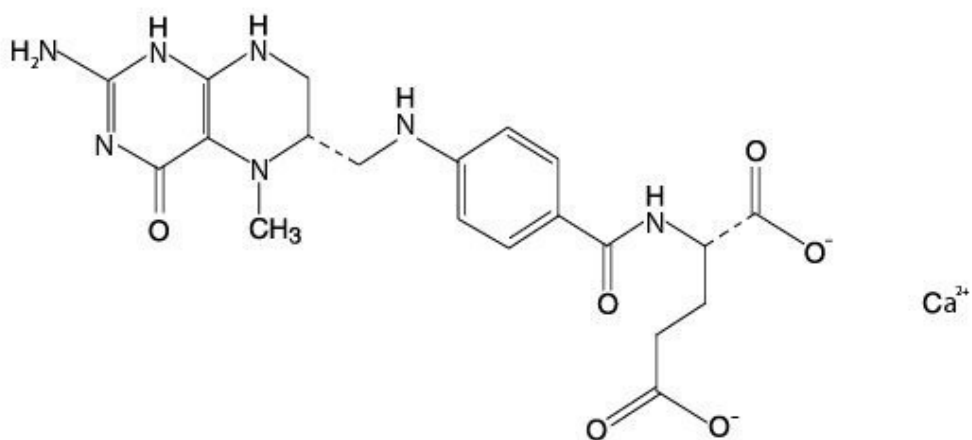
The structural formulas are as follows:



Drospirenone



Ethinyl estradiol



Levomefolate Calcium

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

Drospirenone is a spironolactone analogue with antimineralocorticoid activity. The estrogen in Safyral is ethinyl estradiol (EE).

Contraception

No specific pharmacodynamic studies were conducted with Safyral.

Folate Supplementation

Two studies evaluated the impact of Safyral on plasma folate and red blood cell (RBC) folate levels. A randomized, double-blind, active-controlled, parallel group study compared plasma folate and RBC folate levels during a 24-week treatment with 3 mg DRSP/0.02 mg EE (YAZ) + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population. The pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). [See *Clinical Studies*, 14.4.]

12.3 Pharmacokinetics

Absorption

Safyral and Yasmin are bioequivalent with respect to DRSP and EE.

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of Safyral, which is a combination tablet of DRSP and EE stabilized by betadex as a clathrate (molecular inclusion complex), has not been evaluated. The bioavailability of EE is similar when dosed via a betadex clathrate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1-2 hours after administration of Safyral.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of Yasmin, steady state DRSP concentrations were observed after 8 days. There was about 2 to 3 fold accumulation in serum C_{max} and AUC (0-24h) values of DRSP following multiple dose administration of Yasmin (see Table 1).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of Yasmin serum C_{max} and AUC (0-24h) values of EE accumulate by a factor of about 1.5 to 2 (see Table I).

Levomefolate calcium is structurally identical to L-5-methyltetrahydrofolate (L-5-methyl-THF), a metabolite of vitamin B₉. Mean baseline concentrations of about 15 nmol/L are reached in populations without folate food fortification under normal nutritional conditions. Orally administered levomefolate calcium is absorbed and is incorporated into the body folate pool. Peak plasma concentrations of about 50 nmol/L above baseline are reached within 0.5 – 1.5 hours after single oral administration of 0.451 mg levomefolate calcium.

Steady state conditions for total folate in plasma after intake of 0.451 mg levomefolate calcium are reached after about 8-16 weeks depending on the baseline levels. In red blood cells achievement of steady state is delayed due to the long life-span of red blood cells of about 120 days.

TABLE 1: MEAN PHARMACOKINETIC PARAMETERS OF YASMIN
(DRSP 3 mg and EE 0.03 mg)

DRSP Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{max} (ng/mL)	T_{max} (h)	AUC(0-24h) (ng•h/mL)	t_{1/2} (h)
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA
1/21	12	87.5 (59)	1.7 (20)	827 (23)	30.9 (44)
6/21	12	84.2 (19)	1.8 (19)	930 (19)	32.5 (38)
9/21	12	81.3 (19)	1.6 (38)	957 (23)	31.4 (39)
13/21	12	78.7 (18)	1.6 (26)	968 (24)	31.1 (36)
EE Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{max} (ng/mL)	T_{max} (h)	AUC(0-24h) (ng•h/mL)	t_{1/2} (h)
1/1	11	53.5 (43)	1.9 (45)	280 (87)	NA
1/21	11	92.1 (35)	1.5 (40)	461 (94)	NA
6/21	11	99.1 (45)	1.5 (47)	346 (74)	NA
9/21	11	87 (43)	1.5 (42)	485 (92)	NA
13/21	10	90.5 (45)	1.6 (38)	469 (83)	NA

NA – Not available

Food Effect

The rate of absorption of DRSP and EE following single administration of a formulation similar to Safyral was slower under fed (high fat meal) conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

The effect of food on absorption of levomefolate calcium following administration of Safyral has not been evaluated.

Distribution

DRSP and EE serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4–5 L/kg.

DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Biphasic kinetics is reported for folates with a fast- and a slow-turnover pool. The fast-turnover pool, probably reflecting newly absorbed folate, is consistent with the terminal half-life of approximately 4-5 hours after single oral administration

of 0.451 mg levomefolate calcium. The slow-turnover pool reflecting turnover of folate polyglutamate has a mean residence time of greater than or equal to 100 days.

Metabolism

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by Cytochrome P450 3A4 (CYP3A4).

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver is responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

L-5-methyl-THF is the predominant folate transport form in blood under physiological conditions and during folic acid and levomefolate calcium administration.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38-47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17-20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

L-5-methyl-THF is eliminated from the body by urinary excretion of intact folates and catabolic products as well as fecal excretion through a biphasic kinetics process.

Specific Populations

Pediatric Use: Safety and efficacy of Safyral has been established in women of reproductive age. Safety and efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated. [See *Use in Specific Populations* (8.4).]

Geriatric Use: Safyral has not been studied in postmenopausal women and is not indicated in this population. [See *Use in Specific Populations* (8.5).]

Race: No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (age 25-35) when 3 mg DRSP/0.02 mg EE was administered daily for 21 days. Other ethnic groups have not been specifically studied.

Renal Impairment: Safyral is contraindicated in patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30-65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study 7 subjects continued the use of potassium sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CL_{Cr}, 50-80 mL/min) were comparable to those in the group with normal renal function (CL_{Cr}, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL_{Cr}, 30-50 mL/min) compared to those in the group with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. [see *Contraindications* (4), *Warnings and Precautions* (5.2) and *Use in Specific Populations* (8.6)]

Hepatic Impairment: Safyral is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Safyral has not been studied in women with severe hepatic impairment [see *Contraindications* (4), *Warnings and Precautions* (5.2) and *Use in Specific Populations* (8.7)].

Drug Interactions

Effects of Other Drugs on Combined Hormonal Contraceptives:

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. [See *Drug Interactions* (7.1).]

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin with certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels. [See *Drug Interactions* (7.1).]

HIV Protease Inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. [See *Drug Interactions* (7.1).]

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids. [See *Drug Interactions* (7.1).]

Effects of Combined Oral Contraceptives on Other Drugs:

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations. [See *Drug Interactions* (7.2).]

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies. In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*. [See *Drug Interactions* (7.2).]

Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. [See *Drug Interactions* (7.2).]

Interactions With Drugs That Have the Potential to Increase Serum Potassium:

There is a potential for an increase in serum potassium in women taking Safyral with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2)].

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple time points over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

Effects of Folates on Other Drugs:

There is a potential that folates such as folic acid and levomefolate calcium may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs (e.g., antiepileptics, methotrexate). [See *Drug Interactions* (7.4).]

Effects of other Drugs on Folate:

Several drugs (e.g., methotrexate, sulfasalazine, cholestyramine, antiepileptics) have been reported to reduce folate levels. [See *Drug Interactions* (7.5).]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the hardyian gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate. Mutagenesis studies for levomefolate were conducted *in vitro* and *in vivo* and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Oral Contraceptive Clinical Trial

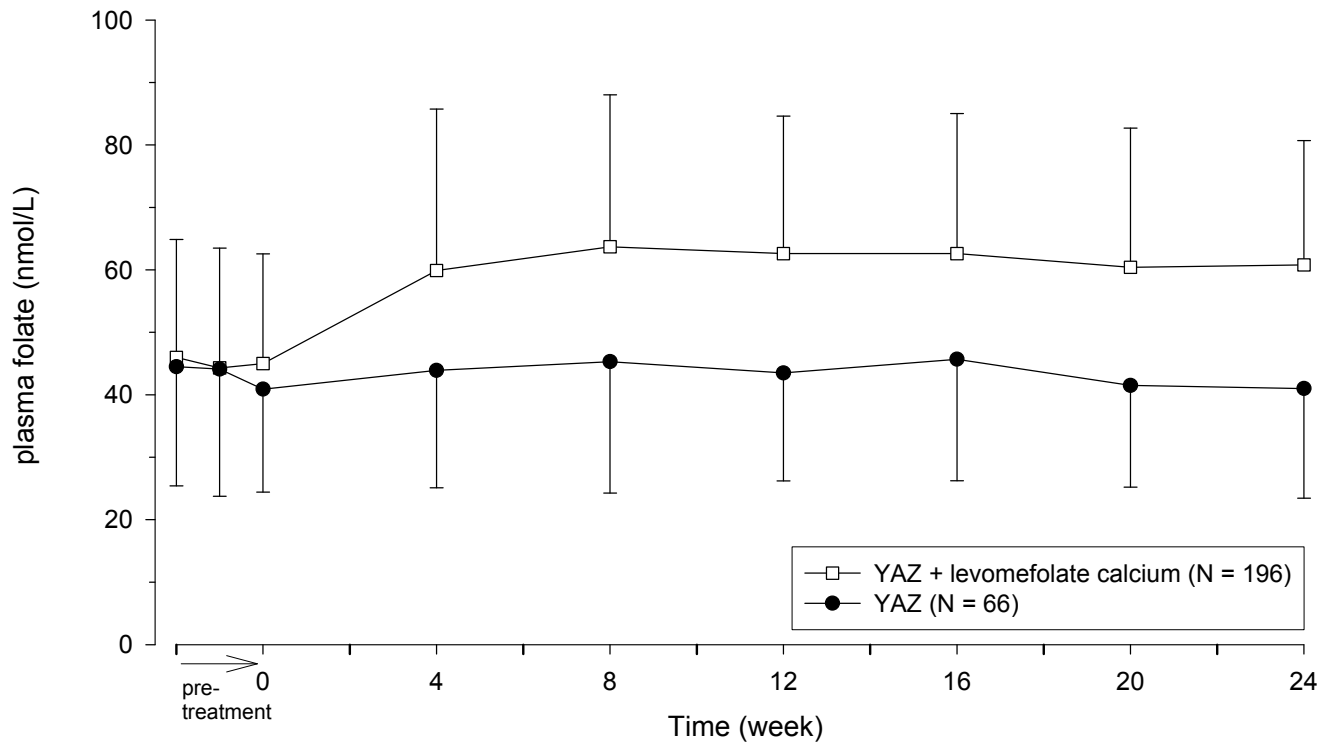
In clinical efficacy studies of YASMIN (3 mg DRSP/0.03 mg EE) of up to 2 years duration, 2,629 subjects completed 33,160 cycles of use without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16 to 37 years. The racial demographic was: 83% Caucasian, 1% Hispanic, 1% Black, <1% Asian, <1% other, <1% missing data, 14% not inquired and <1% unspecified. Pregnancy rates in the clinical trials were less than one per 100 woman-years of use.

14.2 Folate Supplementation Clinical Trials

The development program for Safyral (Yasmin + levomefolate calcium) consisted of two clinical trials.

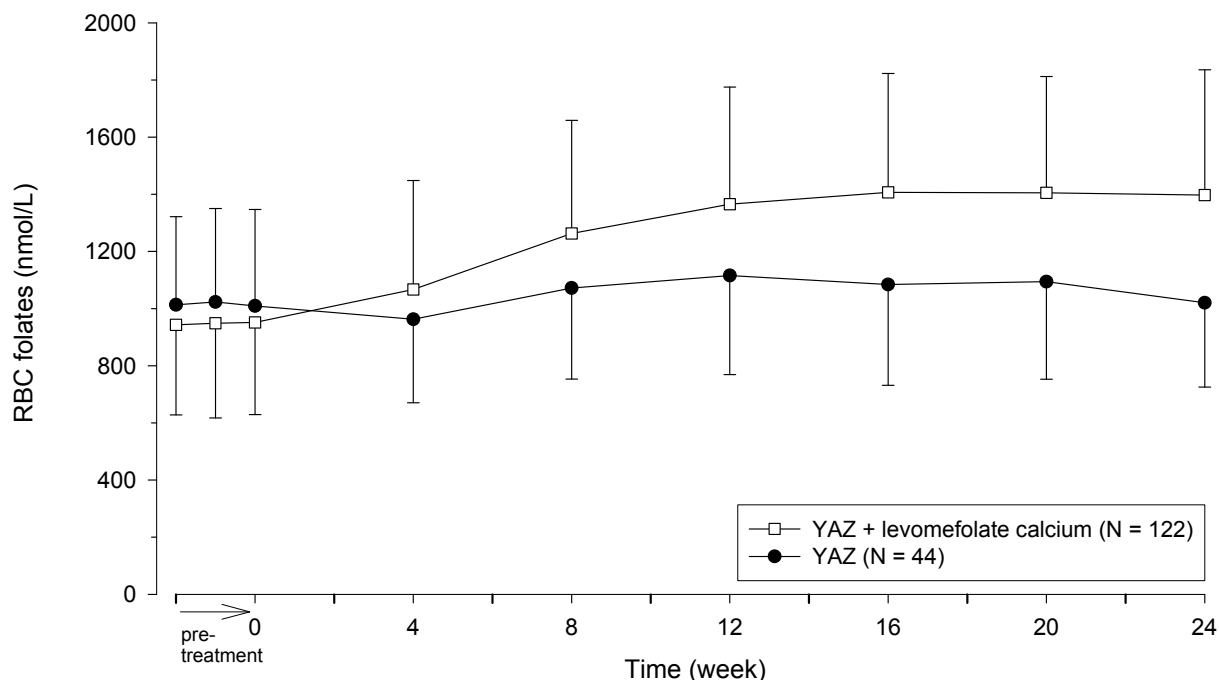
One study was a multicenter, randomized, double-blind, active-controlled, parallel group US study. Plasma folate and red blood cell folate levels were investigated during a 24-week treatment with 3 mg DRSP/0.02 mg EE (YAZ) + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population that consumed folate fortified food. A total of 379 healthy women between 18 and 40 years of age with no restrictions on folate supplementation received YAZ + levomefolate calcium (N= 285) or YAZ (N=94). The plasma and RBC folate concentrations at Week 24 were the co-primary endpoints. Figures 1 and 2 display the results for plasma and RBC folate concentrations, respectively, among evaluable subjects in each arm of the study.

Figure 1: US Study: Mean trough concentration-time curves (and SD) of plasma folates after daily oral administration of YAZ + levomefolate calcium and YAZ



Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on the per protocol analysis populations. The SD bars shown represent one SD.

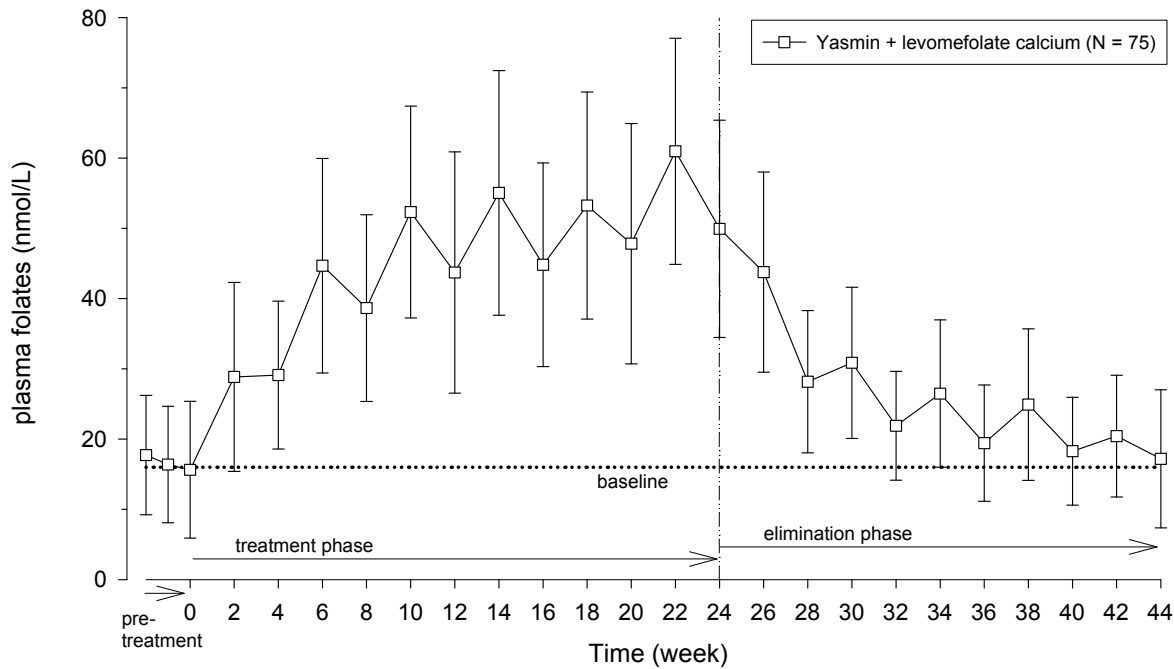
Figure 2: US Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of YAZ + levomefolate calcium and YAZ



Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on the per protocol analysis populations. The SD bars shown represent one SD.

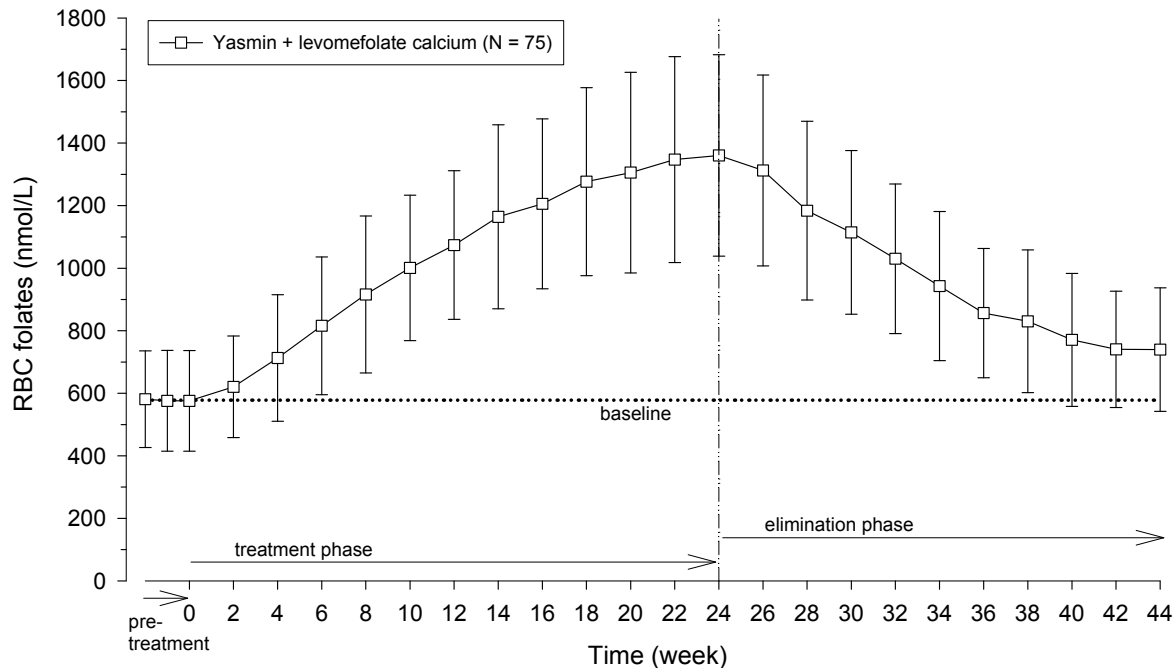
In the second study, the pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). One-hundred and seventy-two healthy women between 18 to 40 years of age from a German population that consumed food without folate fortification and without concomitant intake of folate supplements were randomized to one of the two treatments. Figures 3 and 4 display the results for plasma and RBC folate concentrations, respectively, among evaluable subjects in the levomefolate arm of the study.

Figure 3: German Study: Mean trough concentration-time curve (and SD) of plasma folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on the per protocol analysis population. The SD bars shown represent one SD.

Figure 4: German Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on the per protocol analysis population. The SD bars shown represent one SD.

The potential to reduce the incidence of neural tube defects (NTDs) with folate supplementation is well established based on a body of evidence derived from randomized, controlled trials, nonrandomized intervention trials, and observational studies using folic acid. Therefore, the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily^{1,6}.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is available in packages of three blister packs (50419-403-03).

The film-coated tablets are rounded with biconvex faces, one side is embossed with a regular hexagon shape with Y+ or M+.

Each blister pack contains 28 film-coated tablets in the following order:

21 round, biconvex, orange, film-coated tablets with embossed “Y+” in a regular hexagon on one side each containing 3 mg drospirenone, 0.03 mg ethinyl estradiol, and 0.451 mg levomefolate calcium

7 round, biconvex, light orange, film-coated tablets with embossed “M+” in a regular hexagon on one side each containing 0.451 mg levomefolate calcium

16.2 Storage Conditions

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling]

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that Safyral does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Safyral contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their healthcare provider if they have kidney, liver or adrenal disease because the use of Safyral in the presence of these conditions could cause serious heart and health problems. They should also inform their healthcare provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, Heparin or aldosterone antagonists) for a chronic condition.
- Safyral is not indicated during pregnancy. If pregnancy is planned or occurs during treatment with Safyral, further intake must be stopped. However, women should be advised on the continued need of sufficient folate intake.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. *See “What to Do if You Miss Pills” section in FDA-Approved Patient Labeling.*
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who have not yet had a period, to use an additional method of contraception until she has taken a orange tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.
- Counsel patients to report whether they are taking folate supplements. Safyral contains the equivalent of 0.4 mg (400 mcg) of folic acid.
- Counsel patients to maintain folate supplementation if they discontinue Safyral due to pregnancy.

Manufactured for Bayer HealthCare Pharmaceuticals Inc.

Wayne, NJ 07470

Manufactured in Germany

WARNING TO WOMEN WHO SMOKE

Do not use Safyral if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What Is Safyral?

Safyral is a birth control pill. It contains two female hormones, a synthetic estrogen called ethinyl estradiol and a progestin called drospirenone. Safyral also contains levomefolate calcium, which is a B vitamin.

The progestin drospirenone may increase potassium. Therefore, you should not take Safyral if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Safyral is right for you, and during the first month that you take Safyral, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin, Advil], naproxen [Aleve and others] when taken long-term and daily for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten, Vasotec, Zestril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Safyral may also be taken by women who elect to use an oral contraceptive, to provide folate supplementation. It is recommended that women of reproductive age supplement their diet with 0.4 mg (400 mcg) of folic acid daily to lower their risk of having a pregnancy with a rare type of birth defect (known as a neural tube defect). The amount of folate contained in Safyral supplements folate in the diet to lower this risk should you become pregnant while taking the drug or shortly after stopping it.

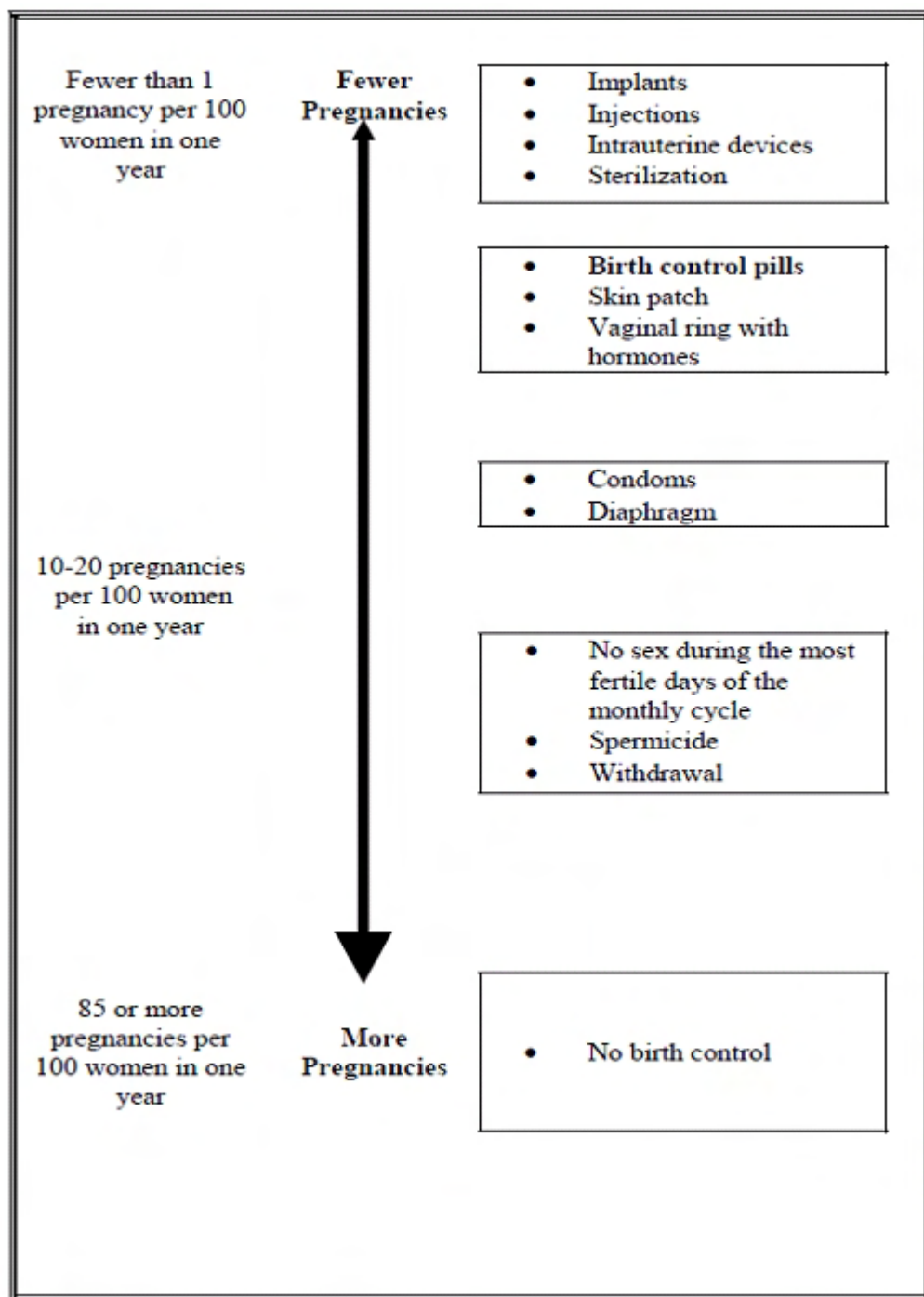
How Well Does Safyral Work?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study, 1 to 2 women out of 100 women, may get pregnant during the first year they use Safyral.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in

effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How Do I Take Safyral?

1. **Be sure to read these directions** before you start taking your pills or anytime you are not sure what to do.
2. The right way to take the pill is to take one pill every day at the same time in the order directed on the package. Preferably, take the pill after the evening meal or at bedtime, with some liquid, as needed. Safyral can be taken without regard to meals.

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.

3. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1-3 packs of pills.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.

4. Missing pills can also cause spotting or light bleeding, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. If you have vomiting (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS." If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

Use a back-up method (such as condoms and spermicides) until you check with your healthcare provider.

6. If you have trouble remembering to take the pill, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

7. If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

Before You Start Taking Your Pills

1. Decide What Time of Day You Want to Take Your Pill

It is important to take Safyral in the order directed on the package at the same time every day, preferably after the evening meal or at bedtime, with some liquid, as needed. Safyral can be taken without regard to meals.

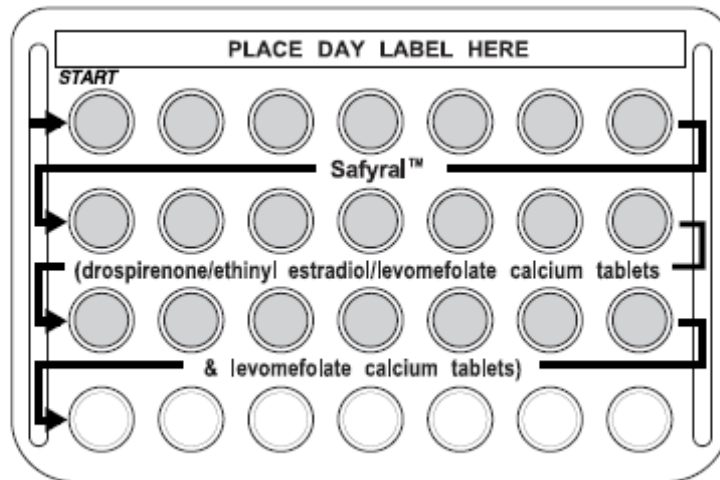
2. Look at Your Pill Pack – It has 28 Pills

The Safyral pill pack has 21 orange pills (with hormones and folate) to be taken for three weeks, followed by 7 light orange pills (without hormones, containing folate) to be taken for one week. **It is important to take the light orange pills because they contain folate.**

3. Also look for:

a) Where on the pack to start taking pills,

b) In what order to take the pills (follow the arrows)



4. Be sure you have ready at all times (a) another kind of birth control (such as condoms or spermicides) to use as a back-up in case you miss pills, and (b) an extra, full pill pack.

When To Start the First Pack of Pills

You have a choice for which day to start taking your first pack of pills. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

Day 1 Start:

1. Take the first orange pill of the pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, because you are starting the Pill at the beginning of your period. However, if you start Safyral later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 orange pills.

Sunday Start:

1. Take the first orange pill of the pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). This also applies if you start Safyral after having been pregnant and you have not had a period since your pregnancy.

When You Switch From a Different Birth Control Pill

When switching from another birth control pill, Safyral should be started on the same day that a new pack of the previous birth control pill would have been started.

When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, Safyral should be started when the next application would have been due. When switching from an injection, Safyral should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Safyral should be started on the day of removal.

What to Do During the Month

1. Take one pill at the same time every day until the pack is empty.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. When you finish a pack of pills, start the next pack on the day after your last light orange pill. **It is important to take the light orange pills because they contain folate.** Do not wait any days between packs.

What to Do if You Miss Pills

If you miss 1 orange pill in Week 1 of your pack:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you miss 2 orange pills in a row in week 1 OR week 2 of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

If you miss 2 orange pills in a row in week 3 or week 4 of your pack:

1. If you are a Day 1 Starter:

Throw out the rest of the pill pack and start a new pack that same day.

2. If you are a Sunday Starter:

Keep taking one pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

3. You could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

4. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.

If you miss 3 or more orange pills in a row during any week:

1. If you are a Day 1 Starter:

Throw out the rest of the pill pack and start a new pack that same day.

2. If you are a Sunday Starter:

Keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

3. You could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

4. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.

If you miss any of the 7 light orange pills in Week 4:

Throw away the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

Finally, if you are still not sure what to do about the pills you have missed:

Use a back-up method (such as condoms and spermicides) anytime you have sex.

Contact your healthcare provider and continue taking one active orange pill each day until otherwise directed.

WHO SHOULD NOT TAKE Safyral?

Your healthcare provider should not give you Safyral if you:

- Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- Have an inherited problem with your blood that makes it clot more than normal
- Have high blood pressure that medicine can't control
- Have diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Have liver disease, including liver tumors
- Have kidney disease
- Have adrenal disease

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are pregnant or suspect you are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider can recommend another method of birth control).

Tell your healthcare provider if you are already taking daily folate supplements.

What Else Should I Know about Taking Safyral?

Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant
- Miss one period and have not taken your birth control pills on time every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

Due to an increased risk of blood clots, you should stop Safyral at least four weeks before you have major surgery and not restart it until at least two weeks after the surgery .

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Safyral, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

If you are currently on daily, long-term treatment for a chronic condition with any of the following medications, you should consult your healthcare provider before taking Safyral:

- NSAIDs (ibuprofen, naproxen and others)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (captopril, enalapril, lisinopril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Tell your healthcare provider about all medicines and herbal products that you take. Some other medicines and herbal products may make birth control pills less effective, including:

- Barbiturates
- Bosentan
- Carbamazepine
- Felbamate
- Griseofulvin
- Oxcarbazepine
- Phenytoin
- Rifampin
- St. John's wort
- Topiramate

Consider using another birth control method when you take medicines (such as the ones listed above) that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Folates may make certain drugs, including some used for epilepsy, less effective, so talk to your healthcare provider about any medicines you take.

If you have vomiting or diarrhea, your birth control pills may not work as well. Take another pill if you vomit within 3-4 hours after taking your pill, or use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

What are the Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are in the:

- Legs (thrombophlebitis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention

- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol; triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know about My Period when Taking Safyral?

Irregular vaginal bleeding or spotting may occur while you are taking Safyral. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long as you have taken the pills regularly on time.

What if I Miss My Scheduled Period when Taking Safyral?

It is not uncommon to miss your period. However, if you miss two periods in a row or miss one period when you have not taken your birth control pills regularly on time, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking Safyral if you are pregnant.

What If I Want to Become Pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill. See your healthcare provider about appropriate folate supplementation if you stop taking Safyral, are pregnant, or plan on becoming pregnant.

General Advice about Safyral

Your healthcare provider prescribed Safyral for you. Please do not share Safyral with anyone else. Keep Safyral out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

Bayer HealthCare Pharmaceuticals Inc.



10.3.3 YAZ

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YAZ safely and effectively. See full prescribing information for YAZ.

YAZ (drospirenone/ethinyl estradiol tablets)

Initial U.S. Approval: 2001

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning

- Women over 35 years old who smoke should not use Yaz (4).
- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)

RECENT MAJOR CHANGES

Warnings and Precautions (5.1, 5.7)

3/2011

INDICATIONS AND USAGE

Yaz is an estrogen/progestin COC, indicated for use by women to:

- Prevent pregnancy. (1.1)
- Treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception. (1.2)
- Treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control. (1.3)

DOSAGE AND ADMINISTRATION

- Take one tablet daily by mouth at the same time every day. (2.1)
- Tablets must be taken in the order directed on the blister pack. (2.1)

DOSAGE FORMS AND STRENGTHS

Yaz consists of 28 film-coated, biconvex tablets in the following order (3):

- 24 light pink tablets, each containing 3 mg drospirenone (DRSP) and 0.02 mg ethinyl estradiol (EE) as betadex clathrate
- 4 white inert tablets

CONTRAINDICATIONS

- Renal impairment or adrenal insufficiency (4)
- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

WARNINGS AND PRECAUTIONS

- Vascular risks: Stop Yaz if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Hyperkalemia: DRSP has antimineralocorticoid activity. Do not use in patients predisposed to hyperkalemia. Check serum potassium level during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium. (5.2, 7.3)
- Liver disease: Discontinue Yaz if jaundice occurs. (5.4)
- High blood pressure: Do not prescribe Yaz for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Yaz. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- Headache: Evaluate significant change in headaches and discontinue Yaz if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

ADVERSE REACTIONS

- The most frequent ($\geq 2\%$) adverse reactions in contraception and acne clinical trials were: headache/migraine (6.7%), menstrual irregularities (4.7%), nausea/vomiting (4.2%), breast pain/tenderness (4.0%) and mood changes (2.2%).
- The most frequent ($\geq 2\%$) adverse reactions in PMDD clinical trials were: menstrual irregularities (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes (for example, CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

USE IN SPECIFIC POPULATIONS

Nursing Mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

1 INDICATIONS AND USAGE

- 1.1 Oral Contraceptive
- 1.2 Premenstrual Dysphoric Disorder (PMDD)
- 1.3 Acne

2 DOSAGE AND ADMINISTRATION

- 2.1 How to Take Yaz
- 2.2 How to Start Yaz
- 2.3 Advice in case of Gastrointestinal Disturbances

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Thromboembolic Disorders and Other Vascular Problems
- 5.2 Hyperkalemia
- 5.3 Carcinoma of the Breasts and Reproductive Organs
- 5.4 Liver Disease
- 5.5 High Blood Pressure
- 5.6 Gallbladder Disease
- 5.7 Carbohydrate and Lipid Metabolic Effects
- 5.8 Headache
- 5.9 Bleeding Irregularities
- 5.10 COC Use Before or During Early Pregnancy
- 5.11 Depression
- 5.12 Interference with Laboratory Tests
- 5.13 Monitoring
- 5.14 Other Conditions

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Other Drugs on Combined Hormonal Contraceptives
- 7.2 Effects of Combined Oral Contraceptives on Other Drugs
- 7.3 Interactions that Have the Potential to Increase Serum Potassium

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Renal Impairment
- 8.7 Patients with Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Oral Contraceptive Clinical Trial
- 14.2 Premenstrual Dysphoric Disorder Clinical Trials
- 14.3 Acne Clinical Trials

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage Conditions

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. [See Contraindications (4)].

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Yaz is indicated for use by women to prevent pregnancy.

1.2 Premenstrual Dysphoric Disorder (PMDD)

Yaz is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of Yaz for PMDD when used for more than three menstrual cycles has not been evaluated.

The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

Yaz has not been evaluated for the treatment of premenstrual syndrome (PMS).

1.3 Acne

Yaz is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. Yaz should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Yaz

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

To achieve maximum contraceptive and PMDD effectiveness, Yaz must be taken exactly as directed. Single missed pills should be taken as soon as remembered.

2.2 How to Start Yaz

Instruct the patient to begin taking Yaz either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start

During the first cycle of Yaz use, instruct the patient to take one light pink Yaz daily, beginning on Day one (1) of her menstrual cycle. (The first day of menstruation is Day one.) She should take one light pink Yaz daily for 24 consecutive days, followed by one white inert tablet daily on days 25 through 28. Yaz should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Yaz can be taken without regard to meals. If Yaz is first taken later than the first day of the menstrual cycle, Yaz should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start

During the first cycle of Yaz use, instruct the patient to take one light pink Yaz daily, beginning on the first Sunday after the onset of her menstrual period. She should take one light pink Yaz daily for 24 consecutive days, followed by one white inert tablet daily on days 25 through 28. Yaz should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Yaz can be taken without regard to meals. Yaz should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Yaz on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her light pink tablets on the next day after ingestion of the last white tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Yaz is started later than the day following administration of the last white tablet, the patient should use another method of contraception until she has taken a light pink Yaz daily for seven consecutive days.

When switching from a different birth control pill

When switching from another birth control pill, Yaz should be started on the same day that a new pack of the previous oral contraceptive would have been started.

When switching from a method other than a birth control pill

When switching from a transdermal patch or vaginal ring, Yaz should be started when the next application would have been due. When switching from an injection, Yaz should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Yaz should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last light pink tablet. If spotting or breakthrough bleeding occurs while taking Yaz, instruct the patient to continue taking her Yaz by the regimen described above. Counsel her that this type of bleeding is usually transient and without significance; however, advise her that if the bleeding is persistent or prolonged, she should consult her healthcare provider.

Although the occurrence of pregnancy is low if Yaz is taken according to directions, if withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Yaz if pregnancy is confirmed.

The risk of pregnancy increases with each active light pink tablet missed. For additional patient instructions regarding missed pills, see the "**WHAT TO DO IF YOU MISS PILLS**" section in the **FDA Approved Patient Labeling** which follows. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more white tablets, she should still be protected against pregnancy provided she begins taking a new cycle of light pink tablets on the proper day.

For postpartum women who do not breastfeed or after a second trimester abortion, start Yaz no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts on Yaz postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Yaz for 7 consecutive days.

2.3 Advice in case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3–4 hours after tablet-taking, this can be regarded as a missed tablet.

3 DOSAGE FORMS AND STRENGTHS

Yaz (drospirenone/ethinyl estradiol tablets) is available in blister packs.

Each blister pack (28 film-coated tablets) contains in the following order:

- 24 light pink tablets each containing 3 mg drospirenone (DRSP) and 0.02 mg ethinyl estradiol (EE) as betadex clathrate
- 4 white inert tablets

4 CONTRAINDICATIONS

Do not prescribe Yaz to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35 [*see Boxed Warning and Warnings and Precautions (5.1)*]
 - Have deep vein thrombosis or pulmonary embolism, now or in the past [*see Warnings and Precautions (5.1)*]
 - Have cerebrovascular disease [*see Warnings and Precautions (5.1)*]
 - Have coronary artery disease [*see Warnings and Precautions (5.1)*]
 - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [*see Warnings and Precautions (5.1)*]
 - Have inherited or acquired hypercoagulopathies [*see Warnings and Precautions (5.1)*]
 - Have uncontrolled hypertension [*see Warnings and Precautions (5.5)*]
 - Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.7)*]
 - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [*see Warnings and Precautions (5.8)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.9)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.3)*]
- Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Yaz if an arterial or venous thrombotic (VTE) event occurs.

The use of COCs increases the risk of venous thromboembolism. However, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs has been estimated to be 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use. Interim data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Interim data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events.

The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Yaz at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Yaz no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Yaz if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. [See *Adverse Reactions* (6).]

Epidemiologic studies including a DRSP-containing COC

Several studies have investigated the relative risks of thromboembolism in women using a different DRSP-containing COC (Yasmin, which contains 0.03 mg of EE and 3 mg of DRSP) compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.^{1,2} The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.

Two additional epidemiological studies, one case-control study (van Hylekama Vlieg et al.³) and one retrospective cohort study (Lidegaard et al.⁴) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

5.2 Hyperkalemia

Yaz contains 3 mg of the progestin DRSP which has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Yaz should not be used in patients with conditions that predispose to hyperkalemia (that is, renal impairment, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Yaz because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Yaz if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Yaz if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Yaz. COCs may decrease glucose intolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COC's.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Yaz develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Yaz if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Based on patient diaries from two contraceptive clinical trials of Yaz, 8 to 25% of women experienced unscheduled bleeding per 28-day cycle. A total of 12 subjects out of 1,056 (1.1%) discontinued due to menstrual disorders including intermenstrual bleeding, menorrhagia, and metrorrhagia.

Women who use Yaz may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from contraception trials for up to 13 cycles, 6 to 10% of women experienced cycles with no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [see Use in Specific Populations (8.1)].

5.11 Depression

Women with a history of depression should be carefully observed and Yaz discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.3)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Contraception and Acne Clinical Trials

The data provided reflect the experience with the use of Yaz in the adequate and well-controlled studies for contraception (N=1,056) and for moderate acne vulgaris (N=536).

For contraception, a Phase 3, multicenter, multinational, open-label study was conducted to evaluate safety and efficacy up to one year in 1,027 women aged 17 – 36 who took at least one dose of Yaz. A second Phase 3 study was a single center, open-label, active-controlled study to evaluate the effect of 7 28-day cycles of Yaz on carbohydrate metabolism, lipids and hemostasis in 29 women aged 18–35. For acne, two multicenter, double-blind, randomized, placebo-controlled studies, in 536 women aged 14–45 with moderate acne vulgaris who took at least one dose of Yaz, evaluated the safety and efficacy during up to 6 cycles.

The adverse reactions seen across the 2 indications overlapped, and are reported using the frequencies from the pooled dataset. The most common adverse reactions ($\geq 2\%$ of users) were: headache/migraine (6.7%), menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia (4.7%), nausea/vomiting (4.2%), breast pain/tenderness (4%) and mood changes (mood swings, depression, depressed mood and affect lability) (2.2%).

PMDD Clinical Trials

Safety data from trials for the indication of PMDD are reported separately due to differences in study design and setting in the Contraception and Acne studies as compared to the PMDD clinical program.

Two (one parallel and one crossover designed) multicenter, double-blind, randomized, placebo-controlled trials for the secondary indication of treating the symptoms of PMDD evaluated safety and efficacy of Yaz during up to 3 cycles among 285 women aged 18–42, diagnosed with PMDD and who took at least one dose of Yaz.

Common adverse reactions ($\geq 2\%$ of users) were: menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia) (24.9%), nausea (15.8%), headache (13%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

Adverse Reactions ($\geq 1\%$) Leading to Study Discontinuation:

Contraception Clinical Trials

Of 1,056 women, 6.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were headache/migraine (1.6%) and nausea/vomiting (1%).

Acne Clinical Trials

Of 536 women, 5.4% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was menstrual irregularities (including menometrorrhagia, menorrhagia, metrorrhagia and vaginal hemorrhage) (2.2%) .

PMDD Clinical Trials

Of 285 women, 11.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were: nausea/vomiting (4.6%), menstrual irregularity (including vaginal hemorrhage, menorrhagia, menstrual disorder, menstruation irregular and metrorrhagia) (4.2%), fatigue (1.8%), breast tenderness (1.4%), depression (1.4%), headache (1.1%), and irritability (1.1%).

Serious Adverse Reactions:

Contraception Clinical Trials: migraine and cervical dysplasia

Acne Clinical Trials: none reported in the clinical trials

PMDD Clinical Trials: cervical dysplasia

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Yaz. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions are grouped into System Organ Classes, and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, retinal thrombosis, myocardial infarction and stroke), hypertension (including hypertensive crisis)

Hepatobiliary disorders: Gallbladder disease, liver function disturbances, liver tumors

Immune system disorders: Hypersensitivity (including anaphylactic reaction)

Metabolism and nutrition disorders: Hyperkalemia, hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance (including diabetes mellitus)

Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme

Gastrointestinal disorders: Inflammatory bowel disease

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase and decrease) in plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP450 enzymes at clinically relevant concentrations [see *Clinical Pharmacology* (12.3)].

7.3 Interactions that Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Yaz with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE (Yasmin) tablets, about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

8.4 Pediatric Use

Safety and efficacy of Yaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Yaz has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Yaz is contraindicated in patients with renal impairment [see *Contraindications* (4) and *Warnings and Precautions* (5.2)].

In subjects with mild renal impairment (creatinine clearance CL_{Cr}, 50–80 mL/min), serum DRSP levels were comparable to those in subjects with normal renal function (CL_{Cr}, >80 mL/min). In subjects with moderate renal impairment (CL_{Cr}, 30–50 mL/min), serum DRSP levels were on average 37% higher than those in the group with normal renal function. In addition, there is a potential to develop hyperkalemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs [see *Clinical Pharmacology* (12.3)].

8.7 Patients with Hepatic Impairment

Yaz is contraindicated in patients with hepatic disease [see *Contraindications (4) and Warnings and Precautions (5.4)*]. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Yaz has not been studied in women with severe hepatic impairment.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

11 DESCRIPTION

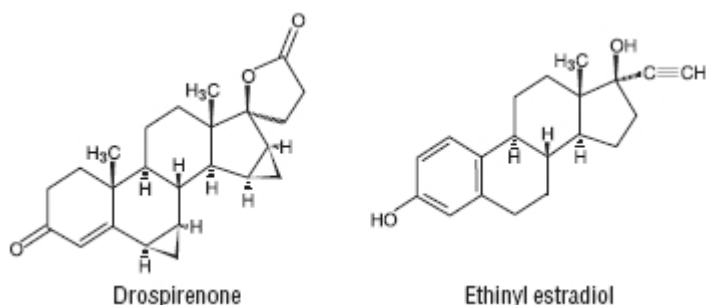
Yaz (drospirenone/ethinyl estradiol tablets) provides an oral contraceptive regimen consisting of 24 light pink active film-coated tablets each containing 3 mg of drospirenone and 0.02 mg of ethinyl estradiol stabilized by betadex as a clathrate (molecular inclusion complex) and 4 white inert film coated tablets.

The inactive ingredients in the light pink tablets are lactose monohydrate NF, corn starch NF, magnesium stearate NF, hypromellose USP, talc USP, titanium dioxide USP, ferric oxide pigment, red NF. The white inert film-coated tablets contain lactose monohydrate NF, corn starch NF, povidone 25000 USP, magnesium stearate NF, hypromellose USP, talc USP, titanium dioxide USP.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11, 12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa- [6,7:15,16]cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of C₂₄H₃₀O₃.

Ethinyl estradiol (19-nor-17 α -pregna 1,3,5(10)-triene-20-yne-3, 17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of C₂₀H₂₄O₂.

The structural formulas are as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and the endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

Drospirenone is a spironolactone analogue with antimineralocorticoid and antiandrogenic activity. The estrogen in Yaz is ethinyl estradiol.

Contraception

Two studies evaluated the effect of 3 mg DRSP / 0.02 mg EE combinations on the suppression of ovarian activity as assessed by measurement of follicle size via transvaginal ultrasound and serum hormone (progesterone and estradiol) analyses during two treatment cycles (21-day active tablet period plus 7-day pill-free period). More than 90% of subjects in these studies demonstrated ovulation inhibition. One study compared the effect of 3 mg DRSP/0.02 mg EE combinations with two different regimens (24-day active tablet period plus 4-day pill-free period vs. 21-day active tablet period plus 7-day pill-free period) on the suppression of ovarian activity during two treatment cycles. During the first treatment cycle, there were no subjects (0/49, 0%) taking the 24-day regimen who ovulated compared to 1 subject (1/50, 2%) using the 21-day regimen. After intentionally introduced dosing errors (3 missed active tablets on Days 1 to 3) during the second treatment cycle, there was 1 subject (1/49, 2%) taking the 24-day regimen who ovulated compared to 4 subjects (4/50, 8%) using the 21-day regimen.

Acne

Acne vulgaris is a skin condition with a multifactorial etiology including androgen stimulation of sebum production. While the combination of EE and DRSP increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established. The impact of the antiandrogenic activity of DRSP on acne is not known.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of Yaz, which is a combination tablet of DRSP and EE stabilized by betadex as a clathrate (molecular inclusion complex), has not been evaluated. The bioavailability of EE is similar when dosed via a betadex clathrate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1–2 hours after administration of Yaz.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1–10 mg. Following daily dosing of Yaz, steady state DRSP concentrations were observed after 8 days. There was about 2 to 3 fold accumulation in serum C_{\max} and AUC (0–24h) values of DRSP following multiple dose administration of Yaz (see Table I).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of Yaz, serum C_{\max} and AUC (0–24h) values of EE accumulate by a factor of about 1.5 to 2 (see Table I).

TABLE I: TABLE OF PHARMACOKINETIC PARAMETERS OF YAZ (DRSP 3 mg and EE 0.02 mg)

DRSP					
Cycle / Day	No. of Subjects	C_{max}^a (ng/mL)	T_{max}^b (h)	AUC(0–24h)^a (ng•h/mL)	t_{1/2}^a (h)
1/1	23	38.4 (25)	1.5 (1–2)	268 (19)	NA ^c
1/21	23	70.3 (15)	1.5 (1–2)	763 (17)	30.8 (22)
EE					
Cycle / Day	No. of Subjects	C_{max}^a (pg/mL)	T_{max}^b (h)	AUC(0–24h)^a (pg•h/mL)	t_{1/2}^a (h)
1/1	23	32.8 (45)	1.5 (1–2)	108 (52)	NA ^c
1/21	23	45.1 (35)	1.5 (1–2)	220 (57)	NA ^c

a) geometric mean (geometric coefficient of variation)

b) median (range)

c) NA = Not available

Food Effect

The rate of absorption of DRSP and EE following single administration of a formulation similar to Yaz was slower under fed (high fat meal) conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

Distribution

DRSP and EE serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4-5 L/kg.

DRSP does not bind to SHBG or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Metabolism

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by Cytochrome P450 3A4 (CYP3A4).

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver is responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38–47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17–20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Specific Populations

Pediatric Use: Safety and efficacy of Yaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated. [See *Use in Specific Populations* (8.4)]

Geriatric Use: Yaz has not been studied in postmenopausal women and is not indicated in this population. [See *Use in Specific Populations* (8.5)]

Race: No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (age 25–35) when 3mg DRSP/0.02 mg EE was administered daily for 21 days. Other ethnic groups have not been specifically studied.

Renal Impairment: Yaz is contraindicated in patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30–65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study, 7 subjects continued the use of potassium sparing drugs for the treatment of their underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CL_{cr}, 50–80 mL/min) were comparable to those in the group with normal renal function (CL_{cr}, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL_{cr}, 30–50 mL/min) compared to those in the group with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. [See *Contraindications* (4), *Warnings and Precautions* (5.2) and *Use in Specific Populations* (8.6).]

Hepatic Impairment: Yaz is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Yaz has not been studied in women with severe hepatic impairment. [see *Contraindications* (4), *Warnings and Precautions* (5.4) and *Use in Specific Populations* (8.7)]

Drug Interactions

Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. [See *Drug Interactions* (7.1).]

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels. [See *Drug Interactions* (7.1).]

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. [See *Drug Interactions* (7.1).]

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids. [See *Drug Interactions* (7.1).]

Effects of Combined Oral Contraceptives on Other Drugs

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the

concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations. [See *Drug Interactions* (7.2) .]

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies. In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4, with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*. [See *Drug Interactions* (7.2) .]

Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. [See *Drug Interactions* (7.2) .]

Interactions With Drugs That Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Yaz with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2)].

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple time points over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the Harderian gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and malignant adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Oral Contraceptive Clinical Trial

In the primary contraceptive efficacy study of Yaz (3 mg DRSP/0.02 mg EE) of up to 1 year duration, 1,027 subjects were enrolled and completed 11,480 28-day cycles of use. The age range was 17 to 36 years. The racial demographic was: 87.8% Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian, and 2.1% other. Women with a BMI greater than 35 were excluded from the trial. The pregnancy rate (Pearl Index) was 1.41 (95% CI [0.73, 2.47]) per 100 woman-years of use based on 12 pregnancies that occurred after the onset of treatment and within 14 days after the last dose of Yaz in women 35 years of age or younger during cycles in which no other form of contraception was used.

14.2 Premenstrual Dysphoric Disorder Clinical Trials

Two multicenter, double-blind, randomized, placebo-controlled studies were conducted to evaluate the effectiveness of Yaz in treating the symptoms of PMDD. Women aged 18–42 who met DSM-IV criteria for PMDD, confirmed by

prospective daily ratings of their symptoms, were enrolled. Both studies measured the treatment effect of Yaz using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable reproductive-aged women with PMDD who were randomly assigned to receive Yaz or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrollment difficulties. A total of 64 women of reproductive age with PMDD were treated initially with Yaz or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.

Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems. Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received Yaz had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking Yaz, compared to 30.0 points in women taking placebo.

14.3 Acne Clinical Trials

In two multicenter, double-blind, randomized, placebo-controlled studies, 889 subjects, ages 14 to 45 years, with moderate acne received Yaz or placebo for six 28-day cycles. The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a "clear" or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) scale on day 15 of cycle 6, as presented in Table II:

Table II: Efficacy Results for Acne Trials*

	Study 1		Study 2	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
ISGA Success Rate	35 (15%)	10 (4%)	46 (21%)	19 (9%)
Inflammatory Lesions				
Mean Baseline Count	33	33	32	32
Mean Absolute (%) Reduction	15 (48%)	11 (32%)	16 (51%)	11 (34%)
Non-inflammatory Lesions				
Mean Baseline Count	47	47	44	44
Mean Absolute (%) Reduction	18 (39%)	10 (18%)	17 (42%)	11 (26%)
Total lesions				
Mean Baseline Count	80	80	76	76
Mean Absolute (%) Reduction	33 (42%)	21 (25%)	33 (46%)	22 (31%)

* Evaluated at day 15 of cycle 6, last observation carried forward for the Intent to treat population

15 REFERENCES

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2. Seeger JD, Loughlin J, Eng PM, et al: Risk of thromboembolism in women taking ethinyl estradiol/drospirenone and other oral contraceptives. *Obstetrics & Gynecology* 2007;110(3):587-593.
3. van Hylekama Vlieg A, Helmerhorst FM, Vandenbroucke JP, et al: The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:b2921.
4. Lidegaard O, Lokkegaard E, Svendsen AL, et al: Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009; 339:b2890.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Yaz (drospirenone/ethinyl estradiol tablets) are available in packages of three blister packs (NDC 50419-405-03).

The film-coated tablets are rounded with biconvex faces, one side is embossed with DS or DP in a regular hexagon.

Each blister pack (28 film-coated tablets) contains in the following order:

- 24 active light pink round, unscored, film-coated tablets debossed with a "DS" in a regular hexagon on one side, each containing 3 mg drospirenone and 0.02 mg ethinyl estradiol
- 4 inert white round, unscored, film-coated tablets debossed with a "DP" in a regular hexagon on one side.

16.2 Storage Conditions

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that the increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.
- Counsel patients that Yaz does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Yaz contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their healthcare provider if they have kidney, liver or adrenal disease because the use of Yaz in the presence of these conditions could cause serious heart and health problems. They should also inform their healthcare provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, heparin or aldosterone antagonists) for a chronic condition.
- Yaz is not indicated during pregnancy. If pregnancy is planned or occurs during treatment with Yaz, further intake must be stopped.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. *See “WHAT TO DO IF YOU MISS PILLS” section in FDA-APPROVED PATIENT LABELING.*
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who have not yet had a period, to use an additional method of contraception until she has taken a light pink tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

Manufactured for



Bayer HealthCare
Pharmaceuticals

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FDA Approved Patient Labeling

Guide for Using Yaz

WARNING TO WOMEN WHO SMOKE

Do not use Yaz if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What Is Yaz?

Yaz is a birth control pill. It contains two female hormones, a synthetic estrogen called ethinyl estradiol and a progestin called drospirenone.

The progestin drospirenone may increase potassium. Therefore, you should not take Yaz if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Yaz is right for you, and during the first month that you take Yaz, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin, Advil], naproxen [Aleve and others] when taken long-term and daily for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten, Vasotec, Zestril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Yaz may also be taken to treat premenstrual dysphoric disorder (PMDD) if you choose to use the Pill for birth control. Unless you have already decided to use the Pill for birth control, you should not start Yaz to treat your PMDD because there are other medical therapies for PMDD that do not have the same risks as the Pill. PMDD is a mood disorder related to the menstrual cycle. PMDD significantly interferes with work or school, or with usual social activities and relationships with others. Symptoms include markedly depressed mood, anxiety or tension, mood swings, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD may include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly before menstruation starts and go away within a few days following the start of the period. Diagnosis of PMDD should be made by healthcare providers.

You should only use Yaz for treatment of PMDD if you:

- Have already decided to use oral contraceptives for birth control, and
- Have been diagnosed with PMDD by your healthcare provider.

Yaz has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious set of symptoms occurring before menstruation. If you or your healthcare provider believe you have PMS, you should take Yaz only if you want to prevent pregnancy; and not for the treatment of PMS.

Yaz may also be taken to treat moderate acne if all of the following are true:

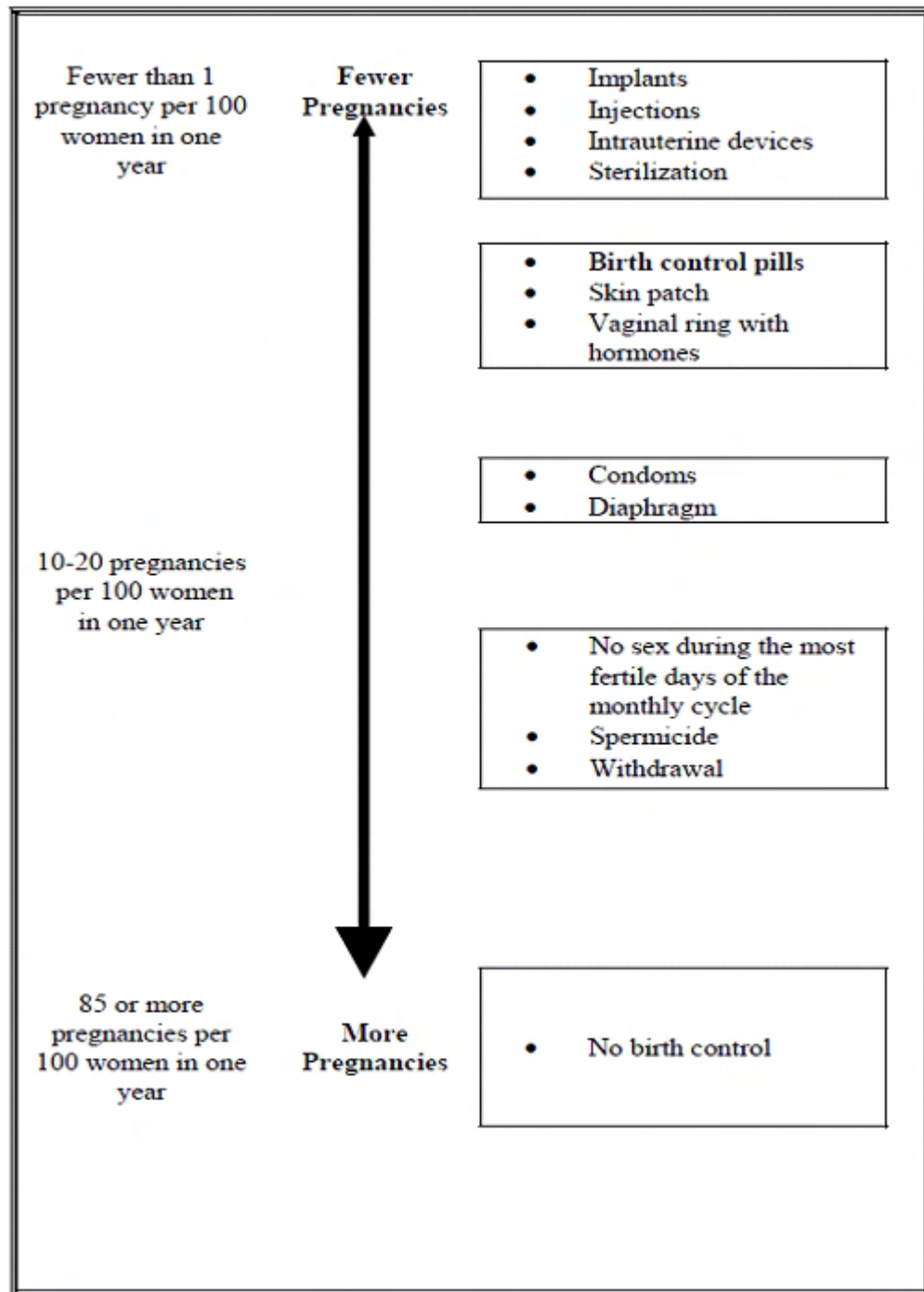
- Your healthcare provider says it is safe for you to use Yaz.
- You are at least 14 years old.
- You have started having menstrual periods.
- You want to use a birth control pill to prevent pregnancy.

How Well Does Yaz Work?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study, 1 to 2 women out of 100 women, may get pregnant during the first year they use Yaz.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How Do I Take Yaz?

1. **Be sure to read these directions** before you start taking your pills or anytime you are not sure what to do.

2. The right way to take the pill is to take one pill every day at the same time in the order directed on the package. Preferably, take the pill after the evening meal or at bedtime, with some liquid, as needed. Yaz can be taken without regard to meals.

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.

3. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1-3 packs of pills.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.

4. Missing pills can also cause spotting or light bleeding, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. If you have vomiting (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS." If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

Use a back-up method (such as condoms and spermicides) until you check with your healthcare provider.

6. If you have trouble remembering to take the pill, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

7. If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

Before You Start Taking Your Pills

1. Decide What Time of Day You Want to Take Your Pill

It is important to take Yaz in the order directed on the package at the same time every day, preferably after the evening meal or at bedtime, with some liquid, as needed. Yaz can be taken without regard to meals.

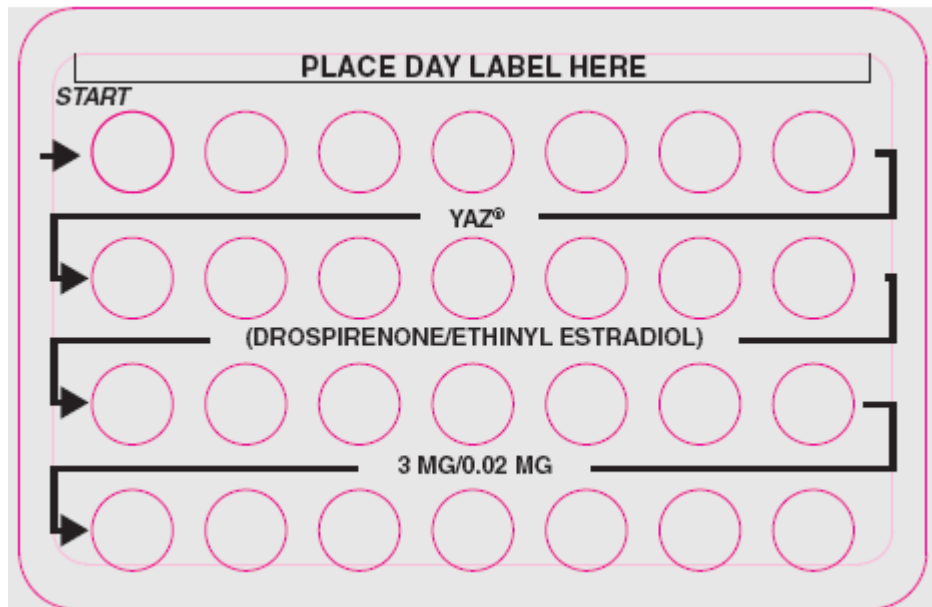
2. Look at Your Pill Pack – It has 28 Pills

The Yaz-pill pack has 24 light pink pills (with hormones) to be taken for 24 days, followed by 4 white pills (without hormones) to be taken for the next four days.

3. Also look for:

a) Where on the pack to start taking pills,

b) In what order to take the pills (follow the arrows)



4. Be sure you have ready at all times (a) another kind of birth control (such as condoms and spermicides) to use as a back-up in case you miss pills, and (b) an extra, full pill pack.

When To Start the First Pack of Pills

You have a choice for which day to start taking your first pack of pills. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

Day 1 Start:

1. Take the first light pink pill of the pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, since you are starting the Pill at the beginning of your period. However, if you start Yaz later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 light pink pills.

Sunday Start:

1. Take the first light pink pill of the pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). This also applies if you start Yaz after having been pregnant, and you have not had a period since your pregnancy.

When You Switch From a Different Birth Control Pill

When switching from another birth control pill, Yaz should be started on the same day that a new pack of the previous birth control pill would have been started.

When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, Yaz should be started when the next application would have been due. When switching from an injection, Yaz should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Yaz should be started on the day of removal.

What to Do During the Month

1. Take one pill at the same time every day until the pack is empty.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. When you finish a pack of pills, start the next pack on the day after your last white pill. Do not wait any days between packs.

What to Do if You Miss Pills

If you miss 1 light pink pill of your pack:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you miss 2 light pink pills in a row in Week 1 or Week 2 of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

If you miss 2 light pink pills in a row in Week 3 or Week 4 of your pack:

1. **If you are a Day 1 Starter:**

Throw out the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:

Keep taking one pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.
3. You may not have your period this month but this is expected. **However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

If you miss 3 or more light pink pills in a row during any week:

1. **If you are a Day 1 Starter:**

Throw out the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:

Keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as condoms and spermicides) as a back-up for those 7 days.
3. **Call your healthcare provider if you miss your period, because you might be pregnant.**

If you miss any of the 4 white pills in Week 4:

Throw away the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

Finally, if you are still not sure what to do about the pills you have missed:

Use a back-up method (such as condoms and spermicides) anytime you have sex.

Contact your healthcare provider and continue taking one active light pink pill each day until otherwise directed.

WHO SHOULD NOT TAKE Yaz?

Your healthcare provider will not give you Yaz if you:

- Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- Have an inherited problem with your blood that makes it clot more than normal
- Have high blood pressure that medicine can't control
- Have diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Have liver disease, including liver tumors
- Have kidney disease
- Have adrenal disease

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are or suspect you are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider can recommend another method of birth control).

What Else Should I Know about Taking Yaz?

Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant

- Miss one period and have not taken your birth control pills every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

You should stop Yaz at least four weeks before you have major surgery and not restart it until at least two weeks after the surgery due to an increased risk of blood clots.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Yaz, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

If you are currently on daily, long-term treatment for a chronic condition with any of the following medications, you should consult your healthcare provider before taking Yaz:

- NSAIDs (ibuprofen, naproxen and others)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (captopril, enalapril, lisinopril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Tell your healthcare provider about all medicines and herbal products that you take. Some other medicines and herbal products may make birth control pills less effective, including:

- Barbiturates
- Bosentan
- Carbamazepine
- Felbamate
- Griseofulvin
- Oxcarbazepine
- Phenytoin
- Rifampin
- St. John's wort
- Topiramate

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

What are the Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start taking birth control pills and when you restart the same or different birth control pills after not using them for a month or more.

It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (thrombophlebitis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol; triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know about My Period when Taking Yaz?

Irregular vaginal bleeding or spotting may occur while you are taking Yaz. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long as you have taken the pills according to direction.

What if I Miss My Scheduled Period when Taking Yaz?

It is not uncommon to miss your period. However, if you miss two periods in a row or miss one period when you have not taken your birth control pills according to directions, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking Yaz if you are pregnant.

What If I Want to Become Pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

General Advice about Yaz

Your healthcare provider prescribed Yaz for you. Please do not share Yaz with anyone else. Keep Yaz out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

Bayer HealthCare Pharmaceuticals Inc.



10.3.4 Beyaz

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Beyaz safely and effectively. See full prescribing information for Beyaz.

BEYAZ (drospirenone/ethinyl estradiol/ levomefolate calcium tablets and levomefolate calcium tablets)

Initial U.S. Approval: 2010

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning

- Women over 35 years old who smoke should not use Beyaz (4).
- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)

INDICATIONS AND USAGE

Beyaz is an estrogen/progestin COC containing a folate, indicated for use by women to:

- prevent pregnancy. (1.1)
- treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception. (1.2)
- treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control. (1.3)
- raise folate levels in women who choose to use an oral contraceptive for contraception. (1.4)

DOSAGE AND ADMINISTRATION

- Take one tablet daily by mouth at the same time every day. (2.1)
- Tablets must be taken in the order directed on the blister pack. (2.1)

DOSAGE FORMS AND STRENGTHS

Beyaz consists of 28 film-coated, biconvex tablets in the following order (3):

- 24 pink tablets, each containing 3 mg drospirenone (DRSP), 0.02 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium
- 4 light orange tablets, each containing 0.451 mg levomefolate calcium

CONTRAINDICATIONS

- Renal impairment or adrenal insufficiency (4)
- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

WARNINGS AND PRECAUTIONS

- Vascular risks: Stop Beyaz if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Hyperkalemia: DRSP has antimineralocorticoid activity. Do not use in patients predisposed to hyperkalemia. Check serum potassium level during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium. (5.2, 7.3)
- Liver disease: Discontinue Beyaz if jaundice occurs. (5.4)
- High blood pressure: Do not prescribe Beyaz for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Beyaz. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- Headache: Evaluate significant change in headaches and discontinue Beyaz if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

ADVERSE REACTIONS

- The most frequent ($\geq 2\%$) adverse reactions in contraception, acne and folate clinical trials were: headache/migraine (5.9%), menstrual irregularities (4.1%), nausea/vomiting (3.5%) and breast pain/tenderness (3.2%).
- The most frequent ($> 2\%$) adverse reactions in PMDD clinical were: menstrual irregularities (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Drugs or herbal products that induce certain enzymes (e.g., CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Not recommended; can decrease milk production. (8.3)

See [17](#) for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling

Revised: 9/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Oral Contraceptive
- 1.2 Premenstrual Dysphoric Disorder (PMDD)
- 1.3 Acne
- 1.4 Folate Supplementation

2 DOSAGE AND ADMINISTRATION

- 2.1 How to Take Beyaz
- 2.2 How to Start Beyaz
- 2.3 Advice in Case of Gastrointestinal Disturbances
- 2.4 Folate Supplementation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Thromboembolic Disorders and Other Vascular Problems
- 5.2 Hyperkalemia
- 5.3 Carcinoma of the Breasts and Reproductive Organs
- 5.4 Liver Disease
- 5.5 High Blood Pressure
- 5.6 Gallbladder Disease
- 5.7 Carbohydrate and Lipid Metabolic Effects
- 5.8 Headache
- 5.9 Bleeding Irregularities
- 5.10 COC Use Before or During Early Pregnancy
- 5.11 Depression
- 5.12 Interference with Laboratory Tests
- 5.13 Monitoring
- 5.14 Other Conditions

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Other Drugs on Combined Hormonal Contraceptives
- 7.2 Effects of Combined Oral Contraceptives on Other Drugs
- 7.3 Interactions that Have the Potential to Increase Serum Potassium
- 7.4 Effects of Folates on Other Drugs
- 7.5 Effects of Other Drugs on Folates

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Renal Impairment
- 8.7 Patients with Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Oral Contraceptive Clinical Trial
- 14.2 Premenstrual Dysphoric Disorder Clinical Trials
- 14.3 Acne Clinical Trials
- 14.4 Folate Supplementation Clinical Trials

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage Conditions

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. [See Contraindications (4)].

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Beyaz is indicated for use by women to prevent pregnancy.

1.2 Premenstrual Dysphoric Disorder (PMDD)

Beyaz is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of Beyaz for PMDD when used for more than three menstrual cycles has not been evaluated.

The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

Beyaz has not been evaluated for the treatment of premenstrual syndrome (PMS).

1.3 Acne

Beyaz is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. Beyaz should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

1.4 Folate Supplementation

Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Beyaz

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

To achieve maximum contraceptive and PMDD effectiveness, Beyaz must be taken as directed. Single missed pills should be taken as soon as remembered.

2.2 How to Start Beyaz

Instruct the patient to begin taking Beyaz either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start

During the first cycle of Beyaz use, instruct the patient to take one pink Beyaz daily, beginning on Day one (1) of her menstrual cycle. (The first day of menstruation is Day one.) She should take one pink Beyaz daily for 24 consecutive days, followed by one light orange tablet daily on days 25 through 28. Beyaz should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Beyaz can be taken without regard to meals. If Beyaz is first taken later than the first day of the menstrual cycle, Beyaz should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start

During the first cycle of Beyaz use, instruct the patient to take one pink Beyaz daily, beginning on the first Sunday after the onset of her menstrual period. She should take one pink Beyaz daily for 24 consecutive days, followed by one light orange tablet daily on days 25 through 28. Beyaz should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Beyaz can be taken without regard to meals. Beyaz should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Beyaz on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her pink tablets on the next day after ingestion of the last light orange folate tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Beyaz is started later than the day following administration of the last light orange tablet, the patient should use another method of contraception until she has taken a pink Beyaz daily for seven consecutive days.

When switching from a different birth control pill

When switching from another birth control pill, Beyaz should be started on the same day that a new pack of the previous oral contraceptive would have been started.

When switching from a method other than a birth control pill

When switching from a transdermal patch or vaginal ring, Beyaz should be started when the next application would have been due. When switching from an injection, Beyaz should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Beyaz should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last pink tablet. If spotting or breakthrough bleeding occurs while taking Beyaz, instruct the patient to continue taking her Beyaz by the regimen described above. Counsel her that this type of bleeding is usually transient and without significance; however, advise her that if the bleeding is persistent or prolonged, she should consult her healthcare provider.

Although the occurrence of pregnancy is low if Beyaz is taken according to directions, if withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Beyaz if pregnancy is confirmed.

The risk of pregnancy increases with each active pink tablet missed. For additional patient instructions regarding missed pills, see the **"WHAT TO DO IF YOU MISS PILLS"** section in the **FDA Approved Patient Labeling** which follows. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more light orange tablets, she should still be protected against pregnancy provided she begins taking a new cycle of pink tablets on the proper day.

For postpartum women who do not breastfeed or after a second trimester abortion, start Beyaz no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts on Beyaz postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Beyaz for 7 consecutive days.

2.3 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, this can be regarded as a missed tablet.

2.4 Folate Supplementation

The U.S. Preventive Services Task Force recommends that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily.¹ Consider other folate supplementation that a woman may be taking before prescribing Beyaz. Ensure that folate supplementation is maintained if a woman discontinues Beyaz due to pregnancy.

3 DOSAGE FORMS AND STRENGTHS

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is available in blister packs.

Each blister pack (28 film-coated tablets) contains in the following order:

- 24 pink tablets each containing 3 mg drospirenone (DRSP), 0.02 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium
- 4 light orange tablets each containing 0.451 mg levomefolate calcium

4 CONTRAINDICATIONS

Do not prescribe Beyaz to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35 [*see Boxed Warning and Warnings and Precautions (5.1)*]
 - Have deep vein thrombosis or pulmonary embolism, now or in the past [*see Warnings and Precautions (5.1)*]
 - Have cerebrovascular disease [*see Warnings and Precautions (5.1)*]
 - Have coronary artery disease [*see Warnings and Precautions (5.1)*]
 - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [*see Warnings and Precautions (5.1)*]
 - Have inherited or acquired hypercoagulopathies [*see Warnings and Precautions (5.1)*]
 - Have uncontrolled hypertension [*see Warnings and Precautions (5.5)*]
 - Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.7)*]
 - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [*see Warnings and Precautions (5.8)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.9)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.3)*]
- Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Beyaz if an arterial or deep venous thrombotic (VTE) event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and

myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Beyaz at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Beyaz no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Beyaz if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. [See *Adverse Reactions* (6).]

Epidemiologic studies including a DRSP-containing COC

Several studies have investigated the relative risks of thromboembolism in women using a different DRSP-containing COC (Yasmin, which contains 0.03 mg of EE and 3 mg of DRSP) compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.^{2,3} The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.

Two additional epidemiological studies, one case-control study (van Hylekama Vlieg et al.⁴) and one retrospective cohort study (Lidegaard et al.⁵) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

5.2 Hyperkalemia

Beyaz contains 3 mg of the progestin DRSP which has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Beyaz should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Beyaz because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Beyaz if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Beyaz if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Beyaz. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Beyaz develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Beyaz if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Data for Beyaz show the average number of episodes of bleeding per reference period (90 days) was 3.2 in Cycles 4-6. The average number of bleeding and/or spotting days with Beyaz was 15.1 days. The intensity of bleeding for Beyaz based on the ratio of spotting-only days versus total bleeding and/or spotting days was 5.2/15.1 days.

Based on patient diaries from two contraceptive clinical trials of YAZ, 8 to 25% of women experienced unscheduled bleeding per 28-day cycle. A total of 12 subjects out of 1,056 (1.1%) discontinued YAZ due to menstrual disorders including intermenstrual bleeding, menorrhagia, and metrorrhagia.

Women who use Beyaz may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from YAZ contraception trials for up to 13 cycles, 6 to 10% of women experienced cycles with no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have),

consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. Discontinue Beyaz if pregnancy is confirmed and initiate a prenatal vitamin containing folate supplementation.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

5.11 Depression

Women with a history of depression should be carefully observed and Beyaz discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

Folates may mask vitamin B12 deficiency.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.3)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Contraception, Acne and Folate Supplementation Clinical Trials

The data provided reflect the experience with the use of YAZ (3 mg DRSP/0.02 mg EE), in the adequate and well-controlled studies for contraception (N=1,056), for moderate acne vulgaris (N=536) and folate supplementation (N=379).

For contraception, a Phase 3, multicenter, multinational, open-label study was conducted to evaluate safety and efficacy up to one year in 1,027 women aged 17-36 who took at least one dose of YAZ. A second Phase 3 study was a single center, open-label, active-controlled study to evaluate the effect of 7 28-day cycles of YAZ on carbohydrate metabolism, lipids and hemostasis in 29 women aged 18-35. For acne, two multicenter, double-blind, randomized, placebo-controlled studies, in 536 women aged 14 – 45 with moderate acne vulgaris who took at least one dose of YAZ, evaluated the safety and efficacy during up to 6 cycles. For folate supplementation, the primary efficacy study using Beyaz was a multicenter, double-blind, randomized, active-controlled US trial in 379 healthy women aged 18- 40 who were treated with Beyaz or YAZ for up to 24 weeks.

The adverse reactions seen across the 3 indications overlapped, and are reported using the frequencies from the pooled dataset. The most common treatment-emergent adverse reactions ($\geq 2\%$ of users) were: headache/migraine (5.9%), menstrual irregularities (including vaginal hemorrhage [primarily spotting], metrorrhagia and menorrhagia) (4.1%), nausea/vomiting (3.5%), and breast pain/tenderness (3.2%).

PMDD Clinical Trials

Safety data from trials for the indication of PMDD are reported separately due to differences in study design and setting in the OC, Acne and Folate Supplementation studies as compared to the PMDD clinical program.

Two (one parallel and one crossover designed) multicenter, double-blind, randomized, placebo-controlled trials for the secondary indication of treating the symptoms of PMDD evaluated safety and efficacy of YAZ during up to 3 cycles among 285 women aged 18 – 42, diagnosed with PMDD and who took at least one dose of YAZ.

Common treatment-emergent adverse reactions ($\geq 2\%$ of users) were: menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia) (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

Adverse Reactions ($>1\%$) Leading to Study Discontinuation:

Contraception Clinical Trials

Of 1,056 women, 6.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were headache/migraine (1.6%) and nausea/vomiting (1.0%).

Acne Clinical Trials

Of 536 women, 5.4% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was menstrual irregularities (including menometrorrhagia, menorrhagia, metrorrhagia and vaginal hemorrhage) (2.2%) .

Folate Clinical Trial

Of 285 women, 4.6% who used Beyaz or YAZ discontinued from the clinical trials due to an adverse reaction; no reaction leading to discontinuation occurred in $\geq 1\%$ of women.

PMDD Clinical Trials

Of 285 women, 11.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were: nausea/vomiting (4.6%), menstrual irregularity (including vaginal hemorrhage, menorrhagia, menstrual disorder, menstruation irregular and metrorrhagia) (4.2%), fatigue (1.8%), breast tenderness (1.4%), depression (1.4%), headache (1.1%), and irritability (1.1%).

Serious Adverse Reactions (Definitely, Probably, or Possibly Related to Study Drug):

Contraception Clinical Trials: migraine and cervical dysplasia

Acne Clinical Trials: none reported in the clinical trials

Folate Supplementation Clinical Trial: cervix carcinoma stage 0

PMDD Clinical Trials: cervical dysplasia

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of YAZ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions are grouped into System Organ Classes, and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, retinal thrombosis, myocardial infarction and stroke), hypertension (including hypertensive crisis)

Hepatobiliary disorders: gallbladder disease, liver function disturbances, liver tumors

Immune system disorders: Hypersensitivity (including anaphylactic reaction)

Metabolism and nutrition disorders: Hyperkalemia, hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance (including diabetes mellitus)

Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme

Gastrointestinal disorders: Inflammatory bowel disease

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

HIV Protease Inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP450 enzymes at clinically relevant concentrations [see *Clinical Pharmacology* (12.3)].

7.3 Interactions that Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Beyaz with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

7.4 Effects of Folates on Other Drugs

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

7.5 Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate levels by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE tablets (Yasmin), about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

Studies to date indicate there is no adverse effect of folate on nursing infants.

8.4 Pediatric Use

Safety and efficacy of Beyaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Beyaz has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Beyaz is contraindicated in patients with renal impairment [see *Contraindications* (4) and *Warnings and Precautions* (5.2)].

Following administration of DRSP 3 mg daily for 14 days, serum DRSP levels in subjects with mild renal impairment (creatinine clearance CL_{Cr}, 50-80 mL/min) were comparable to those in subjects with normal renal function (CL_{Cr}, >80 mL/min). The serum DRSP levels were on average 37 % higher in subjects with moderate renal impairment (CL_{Cr}, 30 - 50 mL/min) compared to those with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33

mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs [see *Clinical Pharmacology* (12.3)].

8.7 Patients with Hepatic Impairment

Beyaz is contraindicated in patients with hepatic disease [see *Contraindications* (4) and *Warnings and Precautions* (5.4)]. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Beyaz has not been studied in women with severe hepatic impairment.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP however, is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Levomefolate calcium doses of 17 mg/day (37-fold higher than the levomefolate calcium dose of Beyaz) were well tolerated after long-term treatment up to 12 weeks.

11 DESCRIPTION

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) provides an oral contraceptive regimen consisting of 28 film-coated tablets that contain the active ingredients specified for each tablet below:

- 24 pink tablets each containing 3 mg DRSP, 0.02 mg EE as betadex clathrate, and 0.451 mg levomefolate calcium
- 4 light orange tablets each containing 0.451 mg levomefolate calcium

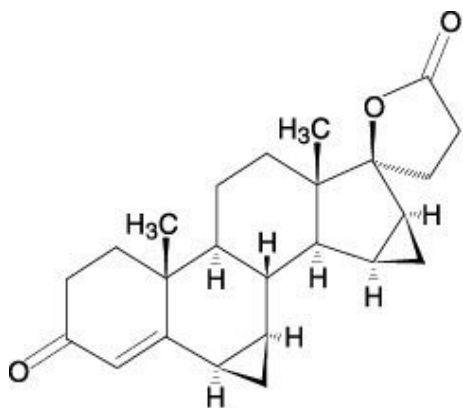
The inactive ingredients in the pink tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose NF, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF, ferric oxide pigment, red NF. The light orange film-coated tablets contain 0.451 mg of levomefolate calcium. The inactive ingredients in the light orange tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose NF, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF, ferric oxide pigment, red NF, ferric oxide pigment, yellow NF.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11, 12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa- [6,7:15,16] cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$.

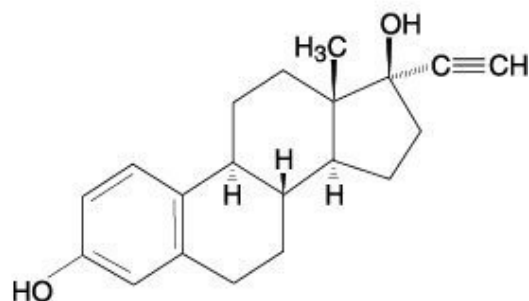
Ethinyl estradiol (19-nor-17 α -pregna 1,3,5(10)-triene-20-yne-3, 17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

Levomefolate calcium (N-[4-[[[2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridiny]methyl]amino]benzoyl]-L-glutamic acid, calcium salt) is a synthetic calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF), which is a metabolite of vitamin B₉ and has a molecular weight of 497.5 and a molecular formula of $C_{20}H_{23}CaN_7O_6$.

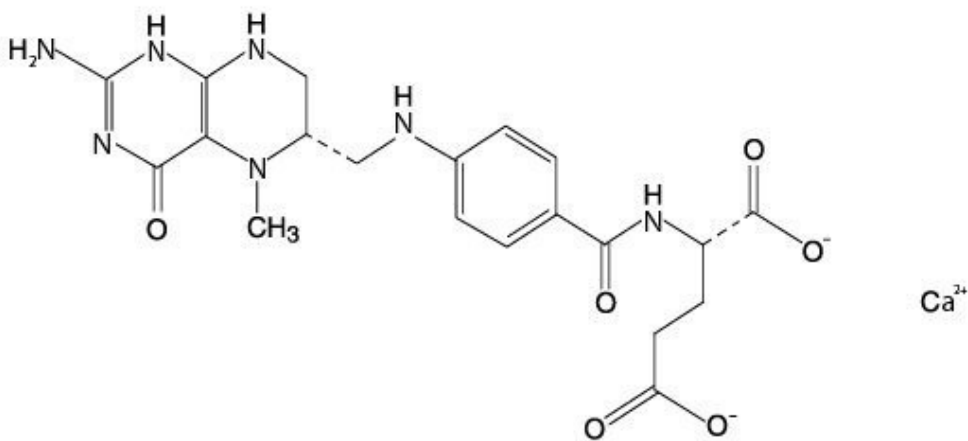
The structural formulas are as follows:



Drospirenone



Ethinyl estradiol



Levomefolate Calcium

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

Drospirenone is a spironolactone analogue with antimineralocorticoid and antiandrogenic activity. The estrogen in Beyaz is ethinyl estradiol.

Contraception

No specific pharmacodynamic studies were conducted with Beyaz.

Acne

Acne vulgaris is a skin condition with a multifactorial etiology including androgen stimulation of sebum production. While the combination of EE and DRSP increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established. The impact of the antiandrogenic activity of DRSP on acne is not known.

Folate Supplementation

Two studies evaluated the impact of Beyaz on plasma folate and RBC folate levels. A randomized, double-blind, active-controlled, parallel group study compared plasma folate and red blood cell (RBC) folate levels during a 24-week treatment with YAZ + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population. The pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). [See *Clinical Studies*, 14.4]

12.3 Pharmacokinetics

Absorption

Beyaz and YAZ are bioequivalent with respect to DRSP and EE.

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of Beyaz, which is a combination tablet of DRSP and EE stabilized by betadex as a clathrate (molecular inclusion complex), has not been evaluated. The bioavailability of EE is similar when dosed via a betadex clathrate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1-2 hours after administration of Beyaz.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of YAZ, steady state DRSP concentrations were observed after 8 days. There was about 2 to 3 fold accumulation in serum C_{max} and AUC (0-24h) values of DRSP following multiple dose administration of YAZ (see Table I).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of YAZ serum C_{max} and AUC (0-24h) values of EE accumulate by a factor of about 1.5 to 2 (see Table I).

Levomefolate calcium is structurally identical to L-5-methyltetrahydrofolate (L-5-methyl-THF), a metabolite of vitamin B₉. Mean baseline concentrations of about 15 nmol/L are reached in populations without folate food fortification under normal nutritional conditions. Orally administered levomefolate calcium is absorbed and incorporated into the body folate pool. Peak plasma concentrations of about 50 nmol/L above baseline are reached within 0.5 – 1.5 hours after single oral administration of 0.451 mg levomefolate calcium.

Steady state conditions for total folate in plasma after intake of 0.451 mg levomefolate calcium are reached after about 8-16 weeks depending on the baseline levels. In red blood cells achievement of steady state is delayed due to the long life-span of red blood cells of about 120 days.

TABLE I: TABLE OF PHARMACOKINETIC PARAMETERS OF YAZ (DRSP 3 mg and EE 0.02 mg)

DRSP					
Cycle / Day	No. of Subjects	C _{max} ^a (ng/mL)	T _{max} ^b (h)	AUC(0-24h) ^a (ng•h/mL)	t _{1/2} ^a (h)
1/1	23	38.4 (25)	1.5 (1-2)	268 (19)	NA ^c
1/21	23	70.3 (15)	1.5 (1-2)	763 (17)	30.8 (22)
EE					
Cycle / Day	No. of Subjects	C _{max} ^a (pg/mL)	T _{max} ^b (h)	AUC(0-24h) ^a (pg•h/mL)	t _{1/2} ^a (h)
1/1	23	32.8 (45)	1.5 (1-2)	108 (52)	NA ^c
1/21	23	45.1 (35)	1.5 (1-2)	220 (57)	NA ^c

a) geometric mean (geometric coefficient of variation)

b) median (range)

c) NA = Not available

Food Effect

The rate of absorption of DRSP and EE following single administration of a formulation similar to Beyaz was slower under fed (high fat meal) conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

The effect of food on absorption of levomefolate calcium following administration of Beyaz has not been evaluated.

Distribution

DRSP and EE serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4–5 L/kg.

DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Biphasic kinetics is reported for folates with a fast- and a slow-turnover pool. The fast turnover pool probably reflecting newly absorbed folate is consistent with the terminal half-life of approximately 4 – 5 hours after single oral administration of 0.451 mg levomefolate calcium. The slow-turnover pool reflecting turnover of folate polyglutamate has a mean residence time of greater than or equal to 100 days.

Metabolism

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by Cytochrome P450 3A4 (CYP3A4).

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver is responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

L-5-methyl-THF is the predominant folate transport form in blood under physiological conditions and during folic acid and levomefolate calcium administration.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38-47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17-20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

L-5-methyl-THF is eliminated from the body by urinary excretion of intact folates and catabolic products as well as fecal excretion through a biphasic kinetics process.

Specific Populations

Pediatric Use: Safety and efficacy of Beyaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated. [See Use in Specific Populations (8.4)]

Geriatric Use: Beyaz has not been studied in postmenopausal women and is not indicated in this population. [See Use in Specific Populations (8.5)]

Race: No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (age 25-35) when 3mg DRSP/20 µg EE was administered daily for 21 days. Other ethnic groups have not been specifically studied.

Renal Impairment: Beyaz is contraindicated in patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30-65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study 7 subjects continued the use of potassium sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CL_{Cr}, 50-80 mL/min) were comparable to those in the group with normal renal function (CL_{Cr}, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL_{Cr}, 30-50 mL/min) compared to those in the group with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L [see *Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.7)*].

Hepatic Impairment: Beyaz is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Beyaz has not been studied in women with severe hepatic impairment. [see *Contraindications (4), Warnings and Precautions (5.4) and Use in Specific Populations (8.7)*]

Drug Interactions

Effects of Other Drugs on Combined Hormonal Contraceptives:

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. [See *Drug Interactions (7.1)*.]

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels. [See *Drug Interactions (7.1)*.]

HIV Protease Inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. [See *Drug Interactions (7.1)*.]

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids. [See *Drug Interactions (7.1)*.]

Effects of Combined Oral Contraceptives on Other Drugs:

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations. [See *Drug Interactions (7.2)*.]

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies. In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*. [See *Drug Interactions (7.2)*.]

Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. [See *Drug Interactions* (7.2).]

Interactions With Drugs That Have the Potential to Increase Serum Potassium:

There is a potential for an increase in serum potassium in women taking Beyaz with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2)].

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple time points over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

Effects of Folates on Other Drugs:

There is a potential that folates such as folic acid and levomefolate calcium may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs (e.g., antiepileptics, methotrexate) [See *Drug Interactions* (7.4).]

Effects of other Drugs on Folate:

Several drugs (e.g., methotrexate, sulfasalazine, cholestyramine, antiepileptics) have been reported to reduce folate levels [See *Drug Interactions* (7.5).]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and malignant adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted in vivo and in vitro and no evidence of mutagenic activity was observed.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate. Mutagenesis studies for levomefolate were conducted in vitro and in vivo and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Oral Contraceptive Clinical Trial

In the primary contraceptive efficacy study of YAZ (3 mg DRSP/0.02 mg EE) of up to 1 year duration, 1,027 subjects were enrolled and completed 11,480 28-day cycles of use. The age range was 17 to 36 years. The racial demographic was: 87.8% Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian, and 2.1% other. Women with a BMI greater than 35 were excluded from the trial. The pregnancy rate (Pearl Index) was 1.41 (95% CI [0.73 – 2.47]) per 100 woman-years of use based on 12 pregnancies that occurred after the onset of treatment and within 14 days after the last dose of YAZ in women 35 years of age or younger during cycles in which no other form of contraception was used.

14.2 Premenstrual Dysphoric Disorder Clinical Trials

Two multicenter, double-blind, randomized, placebo-controlled studies were conducted to evaluate the effectiveness of YAZ in treating the symptoms of PMDD. Women aged 18-42 who met DSM-IV criteria for PMDD, confirmed by prospective daily ratings of their symptoms, were enrolled. Both studies measured the treatment effect of YAZ using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable women with PMDD who were randomly assigned to receive YAZ or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrollment difficulties. A total

of 64 women of reproductive age with PMDD were treated initially with YAZ or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.

Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems. Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received YAZ had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking YAZ, compared to 30.0 points in women taking placebo.

14.3 Acne Clinical Trials

In two multicenter, double blind, randomized, placebo-controlled studies, 889 subjects, ages 14 to 45 years, with moderate acne received YAZ or placebo for six 28 day cycles. The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a "clear" or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) scale on day 15 of cycle 6, as presented in Table II:

Table II: Efficacy Results for Acne Trials*

	Study 1		Study 2	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
ISGA Success Rate	35 (15%)	10 (4%)	46 (21%)	19 (9%)
Inflammatory Lesions				
Mean Baseline Count	33	33	32	32
Mean Absolute (%) Reduction	15 (48%)	11 (32%)	16 (51%)	11 (34%)
Non-inflammatory Lesions				
Mean Baseline Count	47	47	44	44
Mean Absolute (%) Reduction	18 (39%)	10 (18%)	17 (42%)	11 (26%)
Total lesions				
Mean Baseline Count	80	80	76	76
Mean Absolute (%) Reduction	33 (42%)	21 (25%)	33 (46%)	22 (31%)

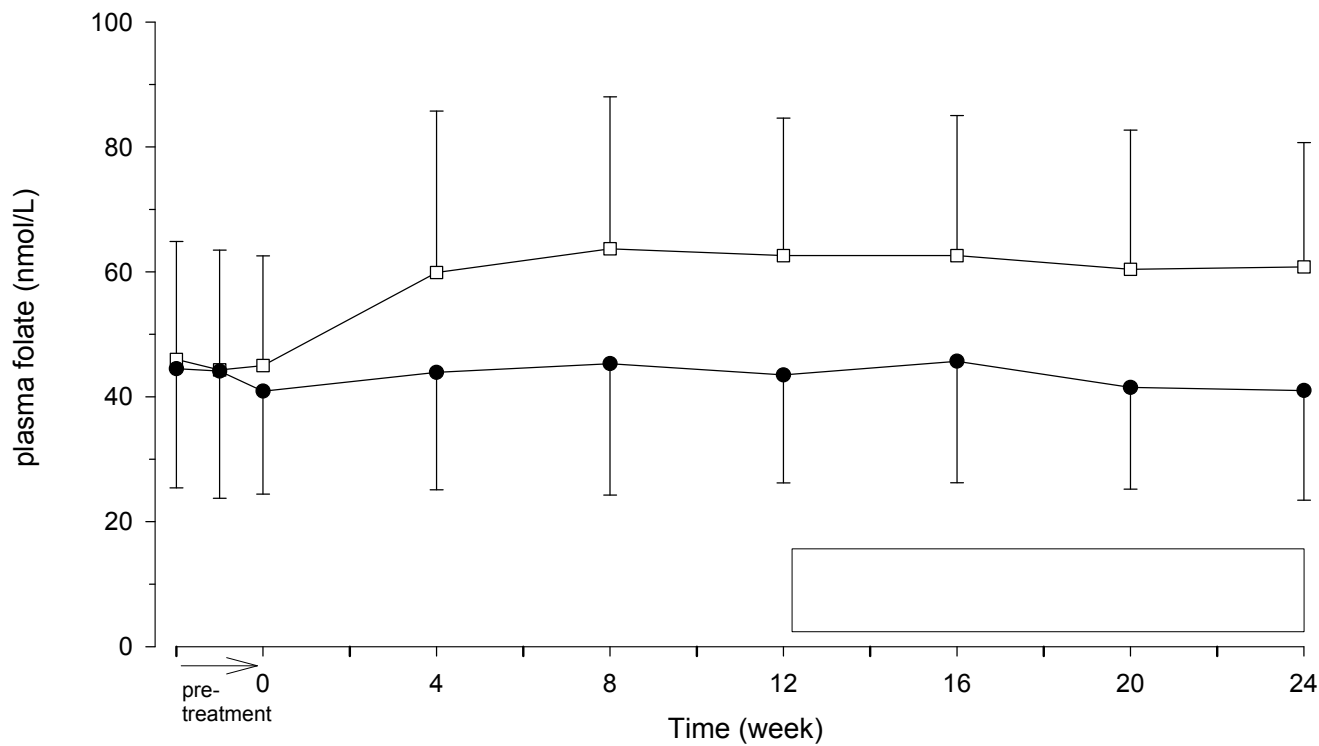
* Evaluated at day 15 of cycle 6, last observation carried forward for the Intent to treat population

14.4 Folate Supplementation Clinical Trials

The development program for Beyaz consisted of two clinical trials.

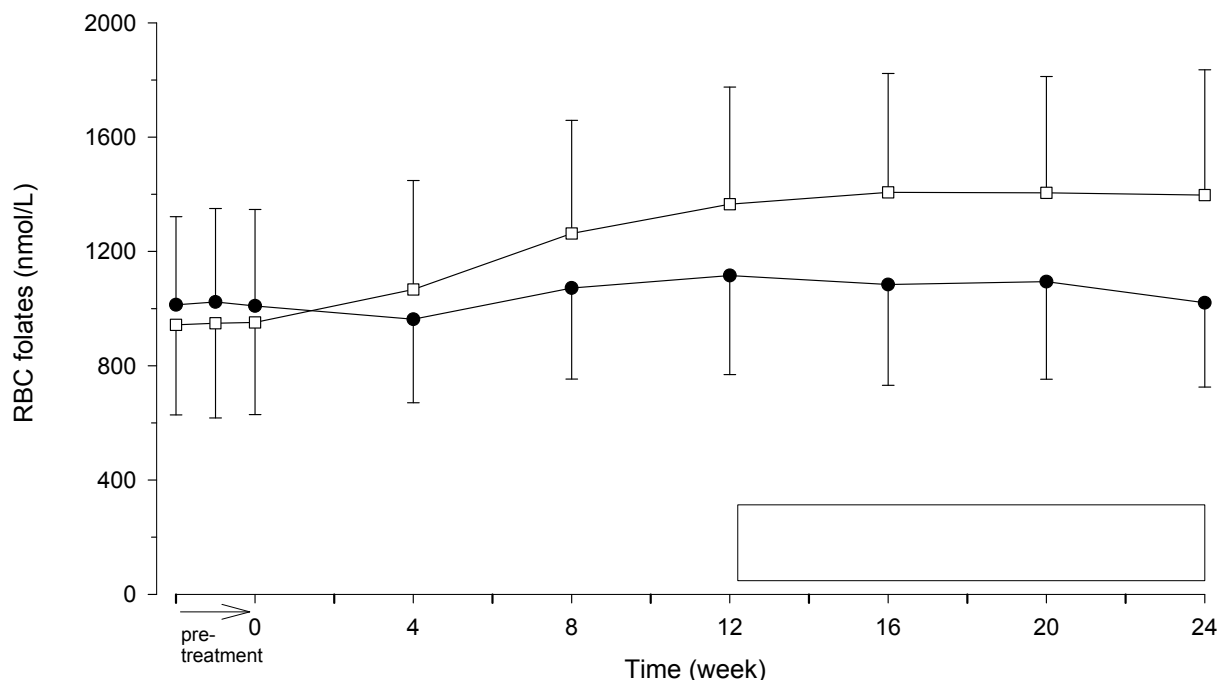
One study was a multicenter, randomized, double-blind, active-controlled, parallel group US study. Plasma folate and red blood cell folate levels were investigated during a 24-week treatment with YAZ + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population with folate fortified food. A total of 379 healthy women between 18 and 40 years of age with no restrictions on folate supplementation received YAZ + levomefolate calcium (N= 285) or YAZ (N=94). The plasma and RBC folate levels at Week 24 were the co-primary endpoints. Figures 1 and 2 display the results for plasma and RBC folate, respectively, among evaluable subjects in each arm of the study.

Figure 1: US Study: Mean concentration-time curves (and SD) of plasma folates after daily oral administration of YAZ + levomefolate calcium and YAZ



Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on per protocol analysis populations. The SD bar shown represents a single SD.

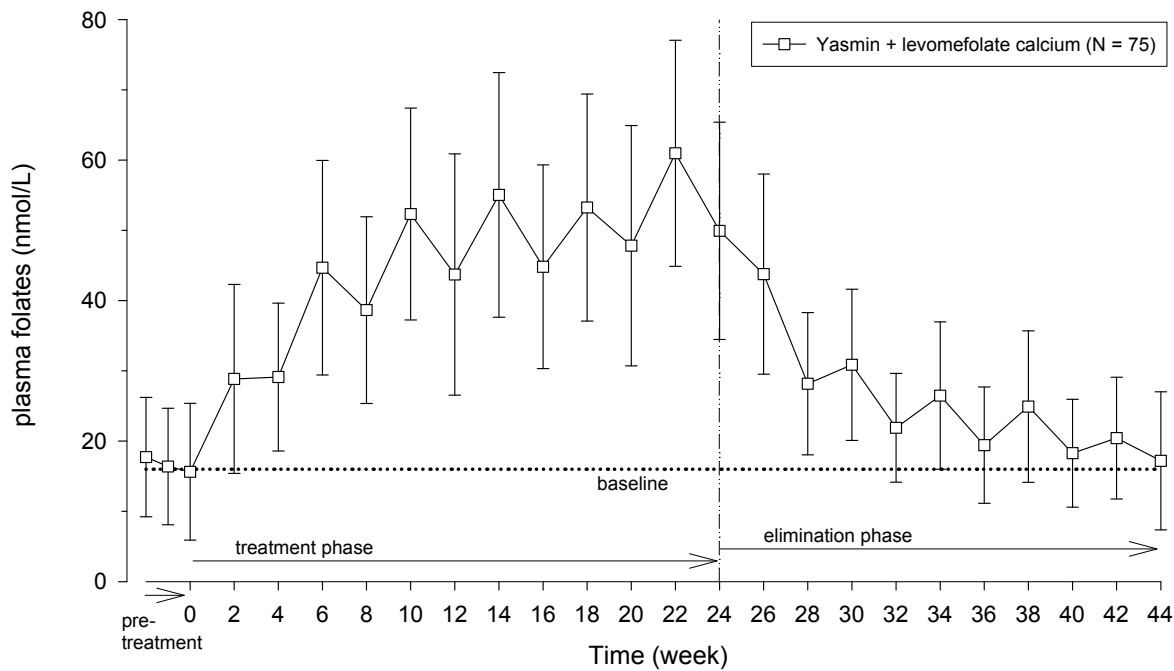
Figure 2: US Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of YAZ + levomefolate calcium and YAZ



Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on per protocol analysis populations. The SD bar shown represents a single SD.

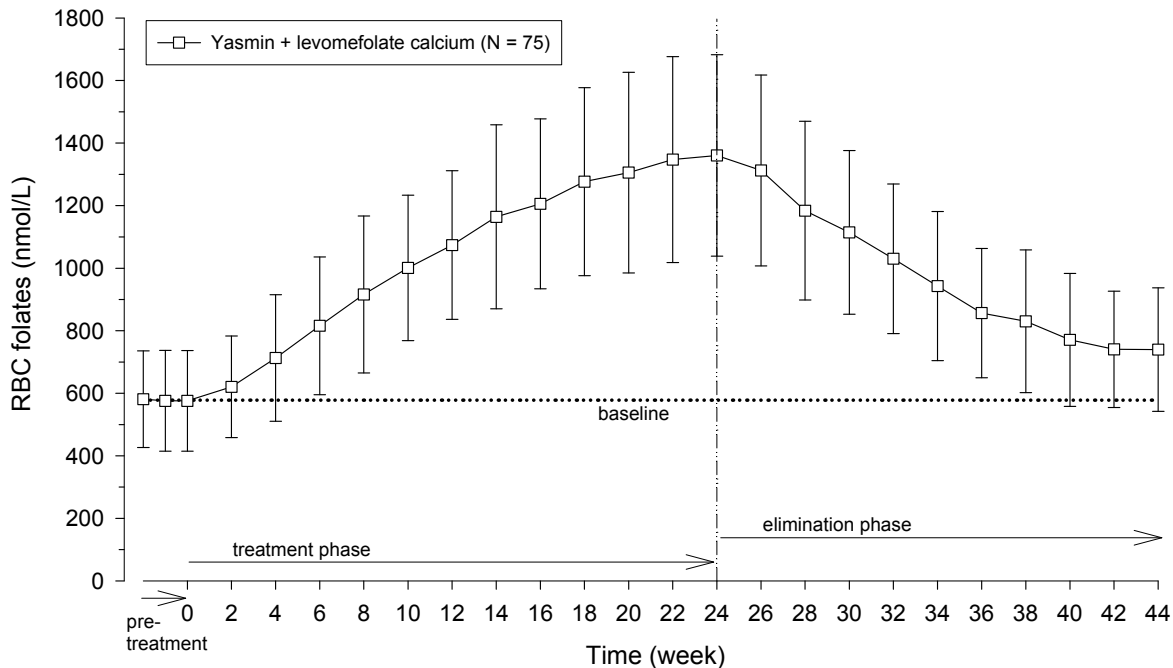
In the second study, the pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). One-hundred and seventy-two healthy women between 18 to 40 years of age from a German population without folate food fortification and without concomitant intake of folate supplements were randomized to one of the two treatments. Figures 3 and 4 display the results for plasma and RBC folate, respectively, among evaluable subjects in the levomefolate arm of the study.

Figure 3: German Study: Mean trough concentration-time curve (and SD) of plasma folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on per protocol analysis populations. The SD bar shown represents a single SD.

Figure 4: German Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on per protocol analysis populations. The SD bar shown represents a single SD.

The potential to reduce the incidence of neural tube defects (NTDs) with folate supplementation is well established based on a body of evidence derived from randomized, controlled trials, nonrandomized intervention trials, and observational studies using folic acid. Therefore, the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily^{1,6}.

15 REFERENCES

1. US Preventive Services Task Force. Folic Acid for the Prevention of Neural Tube Defects: US Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2009;150:626-631.
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6. Centers for Disease Control. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR* 1992;41(No. RR-14):(inclusive page numbers).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) are available in packages of three blister packs (NDC 50419-407-03).

The film-coated tablets are rounded with biconvex faces, one side is embossed with a regular hexagon shape with Z+ or M+.

Each blister pack (28 film-coated tablets) contains in the following order:

- 24 round, biconvex, pink, film-coated tablets with embossed “Z +” in a regular hexagon on one side each containing 3 mg drospirenone, 0.02 mg ethinyl estradiol, and 0.451 mg levomefolate calcium
- 4 round, biconvex, light orange, film-coated tablets with embossed “M+” in a regular hexagon on one side each containing 0.451 mg levomefolate calcium

16.2 Storage Conditions

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling.]

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that Beyaz does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Beyaz contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their health care provider if they have kidney, liver or adrenal disease because the use of Beyaz in the presence of these conditions could cause serious heart and health problems. They should also inform their health care provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, heparin or aldosterone antagonists) for a chronic condition.
- Beyaz is not indicated during pregnancy. If pregnancy is planned or occurs during treatment with Beyaz, further intake must be stopped. However, women should be advised on the continued need of sufficient folate intake.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. *See “What to Do if You Miss Pills” section in FDA-Approved Patient Labeling.*
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum and who have not yet had a period, to use an additional method of contraception until she has taken a pink tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.
- Counsel patients to report whether they are taking folate supplements. Beyaz contains the equivalent of 0.4 mg (400 mcg) of folic acid.
- Counsel patients to maintain folate supplementation if they discontinue Beyaz due to pregnancy.

Manufactured for Bayer HealthCare Pharmaceuticals Inc.

Wayne, NJ 07470

Manufactured in Germany

FDA Approved Patient Labeling

Guide for Using Beyaz

WARNING TO WOMEN WHO SMOKE

Do not use Beyaz if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What Is Beyaz?

Beyaz is a birth control pill. It contains two female hormones, a synthetic estrogen called ethinyl estradiol and a progestin called drospirenone. Beyaz also contains levomefolate calcium, which is a B vitamin.

The progestin drospirenone may increase potassium. Therefore, you should not take Beyaz if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Beyaz is right for you, and during the first month that you take Beyaz, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin, Advil], naproxen [Aleve and others] when taken long-term and daily for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten, Vasotec, Zestril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Beyaz may also be taken to treat premenstrual dysphoric disorder (PMDD) if you choose to use the Pill for birth control. Unless you have already decided to use the Pill for birth control, you should not start Beyaz to treat your PMDD because there are other medical therapies for PMDD that do not have the same risks as the Pill. PMDD is a mood disorder related to the menstrual cycle. PMDD significantly interferes with work or school, or with usual social activities and relationships with others. Symptoms include markedly depressed mood, anxiety or tension, mood swings, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD may include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly before menstruation starts and go away within a few days following the start of the period. Diagnosis of PMDD should be made by healthcare providers.

You should only use Beyaz for treatment of PMDD if you:

- Have already decided to use oral contraceptives for birth control, and

- Have been diagnosed with PMDD by your healthcare provider.

Beyaz has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious set of symptoms occurring before menstruation. If you or your healthcare provider believe you have PMS, you should take Beyaz only if you want to prevent pregnancy; and not for the treatment of PMS.

Beyaz may also be taken to treat moderate acne if all of the following are true:

- Your healthcare provider says it is safe for you to use Beyaz.
- You are at least 14 years old.
- You have started having menstrual periods.
- You want to use a birth control pill to prevent pregnancy.

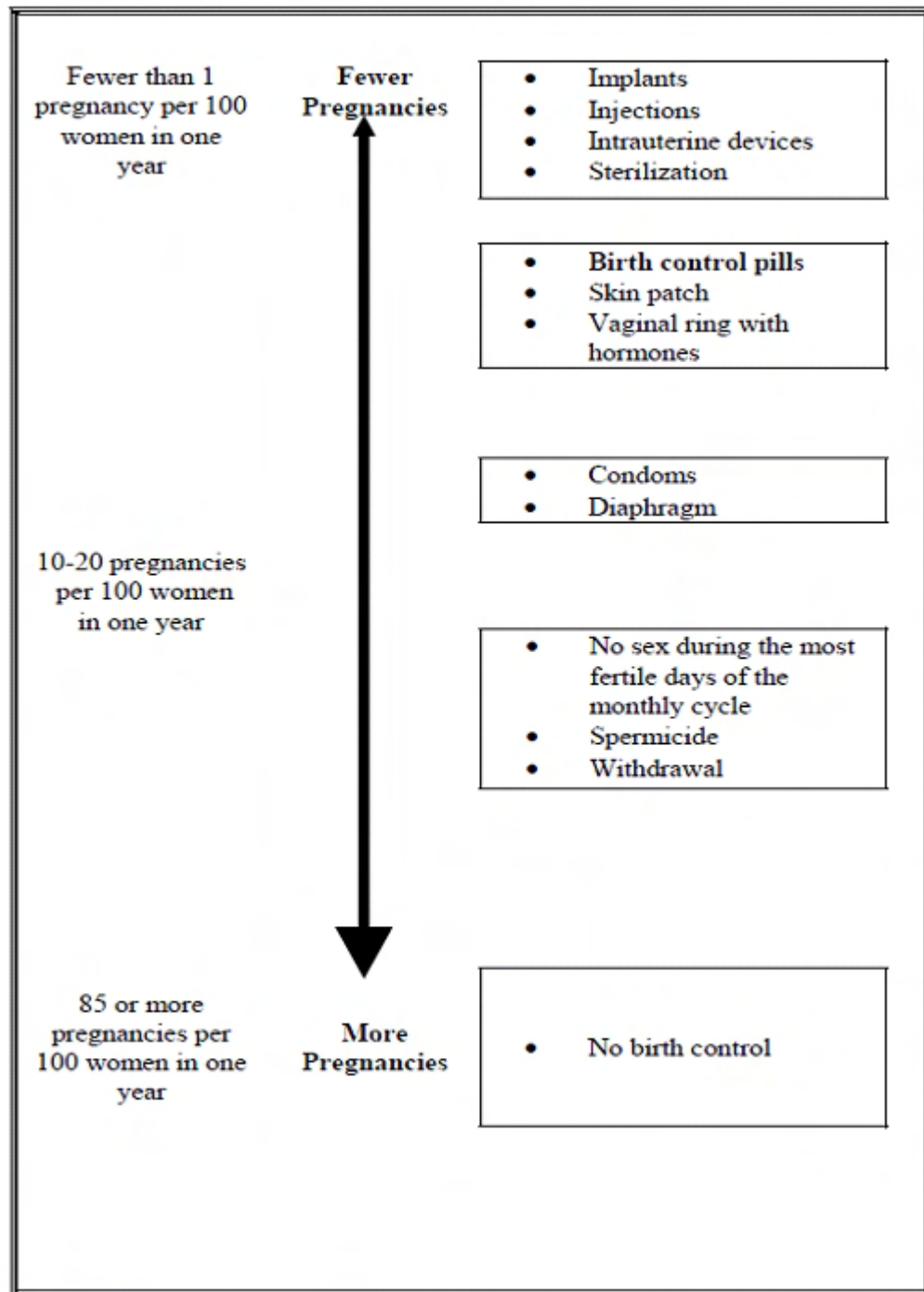
Beyaz may also be taken to provide folate supplementation in women who elect to use an oral contraceptive. It is recommended that women of reproductive age supplement their diet with 0.4 mg (400 mcg) of folic acid daily to lower their risk of having a pregnancy with a rare type of birth defect (known as a neural tube defect). The amount of folate contained in Beyaz supplements folate in the diet to lower this risk should you become pregnant while taking the drug or shortly after stopping it.

How Well Does Beyaz Work?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study, 1 to 2 women out of 100 women, may get pregnant during the first year they use Beyaz.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How Do I Take Beyaz?

1. **Be sure to read these directions** before you start taking your pills or anytime you are not sure what to do.

2. The right way to take the pill is to take one pill every day at the same time in the order directed on the package. Preferably, take the pill after the evening meal or at bedtime, with some liquid, as needed. Beyaz can be taken without regard to meals.

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.

3. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1-3 packs of pills.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.

4. Missing pills can also cause spotting or light bleeding, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. If you have vomiting (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS." If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

Use a back-up method (such as condoms or spermicides) until you check with your healthcare provider.

6. If you have trouble remembering to take the pill, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

7. If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

Before You Start Taking Your Pills

1. Decide What Time of Day You Want to Take Your Pill

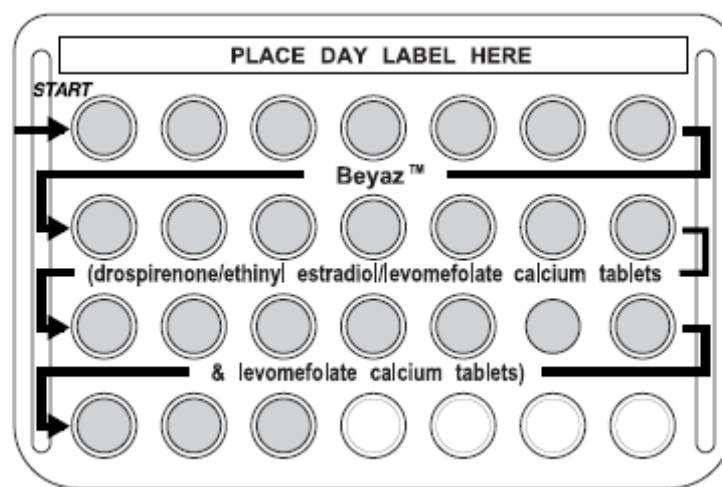
It is important to take Beyaz in the order directed on the package at the same time every day, preferably after the evening meal or at bedtime, with some liquid, as needed. Beyaz can be taken without regard to meals.

2. Look at Your Pill Pack – It has 28 Pills

The Beyaz-pill pack has 24 pink pills (with hormones and folate) to be taken for 24 days, followed by 4 light orange pills (without hormones, containing folate) to be taken for the next four days. **It is important to take the light orange pills because they contain folate.**

3. Also look for:

- a) Where on the pack to start taking pills,
- b) In what order to take the pills (follow the arrows)



4. Be sure you have ready at all times (a) another kind of birth control (such as condoms or spermicides) to use as a back-up in case you miss pills, and (b) an extra, full pill pack.

When To Start the First Pack of Pills

You have a choice for which day to start taking your first pack of pills. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

Day 1 Start:

1. Take the first pink pill of the pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, since you are starting the Pill at the beginning of your period. However, if you start Beyaz later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 pink pills.

Sunday Start:

1. Take the first pink pill of the pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). This also applies if you start Beyaz after having been pregnant, and you have not had a period since your pregnancy.

When You Switch From a Different Birth Control Pill

When switching from another birth control pill, Beyaz should be started on the same day that a new pack of the previous birth control pill would have been started.

When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, Beyaz should be started when the next application would have been due. When switching from an injection, Beyaz should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Beyaz should be started on the day of removal.

What to Do During the Month

1. Take one pill at the same time every day until the pack is empty.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. When you finish a pack of pills, start the next pack on the day after your last light orange pill. **It is important to take the light orange pills because they contain folate.** Do not wait any days between packs.

What to Do if You Miss Pills

If you miss 1 pink pill in Week 1 of your pack:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you miss 2 pink pills in a row in week 1 OR week 2 of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.

3. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

If you miss 2 pink pills in a row in week 3 or week 4 of your pack:

1. **If you are a Day 1 Starter:**

Throw out the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:

Keep taking one pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

3. You may not have your period this month but this is expected. **However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

If you miss 3 or more pink pills in a row during any week:

1. **If you are a Day 1 Starter:**

Throw out the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:

Keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

3. You may not have your period this month but this is expected. **However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

If you miss any of the 4 light orange pills in Week 4:

Throw away the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

Finally, if you are still not sure what to do about the pills you have missed:

Use a back-up method (such as condoms and spermicides) anytime you have sex.

Contact your healthcare provider and continue taking one active pink pill each day until otherwise directed.

WHO SHOULD NOT TAKE Beyaz?

Your healthcare provider will not give you Beyaz if you:

- Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- Have an inherited problem with your blood that makes it clot more than normal

- Have high blood pressure that medicine can't control
- Have diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Have liver disease, including liver tumors
- Have kidney disease
- Have adrenal disease

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are or suspect you are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider can recommend another method of birth control).

Tell your healthcare provider if you are already taking daily folate supplements.

What Else Should I Know about Taking Beyaz?

Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant
- Miss one period and have not taken your birth control pills every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

You should stop Beyaz at least four weeks before you have major surgery and not restart it until at least two weeks after the surgery due to an increased risk of blood clots.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Beyaz, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

If you are currently on daily, long-term treatment for a chronic condition with any of the following medications, you should consult your healthcare provider before taking Beyaz:

- NSAIDs (ibuprofen, naproxen and others)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (captopril, enalapril, lisinopril and others)

- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Tell your healthcare provider about all medicines and herbal products that you take. Some other medicines and herbal products may make birth control pills less effective, including:

- Barbiturates
- Bosentan
- Carbamazepine
- Felbamate
- Griseofulvin
- Oxcarbazepine
- Phenytoin
- Rifampin
- St. John's wort
- Topiramate

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Folates may make certain drugs, including some used for epilepsy, less effective, so talk to your healthcare provider about any medicines you take.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

What are the Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (thrombophlebitis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

- High blood pressure

- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headaches

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol; triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know about My Period when Taking Beyaz?

Irregular vaginal bleeding or spotting may occur while you are taking Beyaz. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long as you have taken the pills according to direction.

What if I Miss My Scheduled Period when Taking Beyaz?

It is not uncommon to miss your period. However, if you miss two periods in a row or miss one period when you have not taken your birth control pills according to directions, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking Beyaz if you are pregnant.

What If I Want to Become Pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill. See your health care provider about appropriate folate supplementation if you stop taking Beyaz, are pregnant, or plan on becoming pregnant.

General Advice about Beyaz

Your healthcare provider prescribed Beyaz for you. Please do not share Beyaz with anyone else. Keep Beyaz out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

Bayer HealthCare Pharmaceuticals Inc.