



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

December 8, 2011

Scott Monroe, MD

Director

Division of Reproductive and Urologic Products

Yasmin

(Bayer HealthCare Pharmaceuticals)

- A combination oral contraceptive (COC) that contains 3 mg drospirenone (DRSP) and 30 µg ethinyl estradiol (EE)
- Approved for marketing in the US in 2001
- First COC to contain the progestin drospirenone

Major Objectives of the Meeting Include

- To learn if Committee members believe, based on available epidemiologic studies, that users of Yasmin and other DRSP-containing COCs are at an increased risk of thrombotic and thromboembolic events compared to users of COCs containing other progestins that have been included in the epidemiologic studies
- To learn if Committee members believe that, in the general population of women, the benefits of Yasmin and other DRSP-containing COCs for prevention of pregnancy outweigh their risks. If not, are there subpopulations of women for whom the risk/benefit profile would be favorable?

Thrombotic and Thromboembolic Events Associated with Use of COCs

- All COCs pose safety concerns, most importantly thrombotic and thromboembolic events (TTEs)
- TTEs, both venous and arterial, are observed more commonly in users of COCs than in non-users
- Rates for TTEs in COC users, however, are lower than the rates in pregnancy and the post-partum period

Role of Estrogen and Progestin in TTE Risk Associated with Use of COCs

- The increased cardiovascular risk associated with the use of COCs was initially attributed to the effect of the estrogenic component. The dose of the estrogen in COCs has been reduced several-fold since their initial approval in the 1960s
- Beginning in the 1990s with the introduction of several new progestins, attention has also focused on the possible role of the progestin component with respect to the TTE risk of COCs

Epidemiologic Studies of TTE Risk in Users of Yasmin

- At the separate requests of the European regulatory agency and the FDA, the Sponsor conducted two post approval epidemiologic studies to assess the cardiovascular risk associated with the use of Yasmin
- Both of the studies, published in 2007, reported no increased risk for TTEs in users of Yasmin compared to users of COCs with progestins other than DRSP
- Since 2009, several studies, including an FDA-funded study, reported an increased TTE risk in users of Yasmin compared to COCs with progestins other than DRSP

Interpretation of Conflicting Epidemiologic Findings regarding TTE Risk is Difficult

- Virtually all published epidemiologic studies regarding the TTE risk of DRSP-containing COCs are based on comparison of Yasmin to other COCs
- Both the FDA and Bayer HealthCare presentations will analyze the conflicting epidemiologic findings
- As with all epidemiologic studies, methodological issues make interpretation of these conflicting results difficult
- Because of these conflicting results, we believe that Advisory Committee discussion and advice are warranted and will be helpful to the Division in any future regulatory actions regarding Yasmin and other DRSP-containing COCs

Overview of the Agenda

- 8:20 FDA: Regulatory History & Overview of Studies
- 8:55 Dr. Sidney: FDA-funded Epidemiologic Study
- 9:10 FDA: Interpretation of Epidemiologic Studies
- 9:30 Questions from Committee to Presenters
- 10:15 Bayer Healthcare Pharmaceuticals Presentations
- 11:45 Questions from Committee to Presenters
- 12:00 Lunch
- 1:00 Open Public Hearing
- 2:00 FDA: Risk/Benefit Analysis Summary
- 2:10 Questions from Committee to Presenters
- 2:30 Committee Discussion and Voting
- 5:00 Adjournment



Introduction and Regulatory History

December 8, 2011

Gerald Willett, MD

Division of Reproductive and Urologic Products

Content of Presentation

- Description of drospirenone (DRSP)-containing combination oral contraceptives (COCs)
- Primary and secondary indications
- Timeline of US regulatory actions and publications on safety in the medical literature
- General comments on COCs and cardiovascular risk in women
- Efficacy of COCs
- Drug utilization information for DRSP-containing COCs

DRSP-Containing COCs

- Ethinyl estradiol (EE)
 - Principal estrogen in almost all COCs
 - Dose relationship to risk of VTE
- Drospirenone (DRSP)
 - Spironolactone analogue with antimineralocorticoid activity (potential effect of hyperkalemia)
 - Antiandrogenic activity

DRSP-Containing COCs

| Product | DRSP | EE | Levomefolate | Regimen |
|---------|------|-------|--------------|---------|
| Yasmin | 3 mg | 30 µg | 0 | 21-day |
| YAZ | 3 mg | 20 µg | 0 | 24-day |
| Beyaz | 3 mg | 20 µg | 0.451 mg | 24-day |
| Safyral | 3 mg | 30 µg | 0.451 mg | 21-day |

DRSP = drospirenone; EE = ethinyl estradiol

Indications

Primary Indication for all products – Prevention of Pregnancy

| Product | Secondary Indications |
|---------|--|
| Yasmin | None |
| YAZ | <ul style="list-style-type: none"> • Treat symptoms of premenstrual dysphoric disorder (PMDD) • Treat moderate acne |
| Beyaz | <ul style="list-style-type: none"> • Treat symptoms of premenstrual dysphoric disorder (PMDD) • Treat moderate acne • Raise folate levels |
| Safyral | <ul style="list-style-type: none"> • Raise folate levels |



Timeline

| 2001 | |
|-------------|---|
| May | Yasmin approved in US |
| 2006 | |
| March | YAZ approved (contraception indication) |
| October | YAZ approved (PMDD secondary indication) |
| 2007 | |
| January | YAZ approved (acne secondary indication) |
| May | Publication of the EURAS study (Europe) reporting no difference in VTE risk |
| September | Publication of the Ingenix study (US) reporting no difference in VTE risk |

Timeline

| 2009 | |
|-----------|---|
| August | Publication of two additional European studies in the <i>British Medical Journal (BMJ)</i> reporting an increased VTE risk |
| 2010 | |
| April | Labeling change in US reflects data from: <ul style="list-style-type: none"> • 2 prospective studies (EURAS and Ingenix) • 2 retrospective studies in BMJ |
| September | Beyaz approved |
| December | Safyral approved |

Timeline

| 2011 | |
|-----------|--|
| April | Publication of two more studies in <i>BMJ</i> (one US, one UK) reporting an increased VTE risk |
| May | Drug Safety Communication: FDA informs the public about all of these publications |
| September | Drug Safety Communication: FDA announces preliminary findings from FDA-funded study of commonly prescribed hormonal contraceptives in the US |
| October | FDA posts final report of FDA-funded study online |

General VTE Risk

- Overall
- Pregnancy & Postpartum
- Associated with COCs

VTE Rates - Reproductive-Age Women (Per 10,000 PY)

| Age Group | DVT only | PE ± DVT | All VTEs |
|-----------|----------|----------|----------|
| 15-19 | 1.8 | 0.8 | 2.7 |
| 20-24 | 4.1 | 1.0 | 5.1 |
| 25-29 | 5.1 | 2.1 | 7.2 |
| 30-34 | 4.6 | 2.9 | 7.5 |
| 35-39 | 3.5 | 4.0 | 7.4 |
| 40-44 | 4.7 | 3.7 | 8.4 |
| 45-49 | 5.1 | 4.5 | 9.6 |

DVT = deep vein thrombosis; PE = pulmonary embolism
Silverstein et al. 1966-1990 Olmstead County, Minnesota

VTE Rates – Pregnancy & Postpartum (Per 10,000 PY)

| Age Group | Pregnancy | Postpartum | Total | Not Pregnant or Post-partum |
|-----------|-----------|------------|-------------|-----------------------------|
| 15-19 | 24.0 | 24.1 | 24.0 | 1.7 |
| 20-24 | 7.1 | 49.0 | 17.6 | 3.5 |
| 25-29 | 5.6 | 54.8 | 17.9 | 4.7 |
| 30-34 | 13.1 | 42.9 | 20.6 | 5.7 |
| ≥ 35 | 14.9 | 89.8 | 33.7 | 6.2 |
| All ages | 9.5 | 51.1 | 20.0 | 4.6 |

Heit et al. 1966-1995 Olmstead County, Minnesota

VTE Risk – COC Users vs. Non-users

- Early studies, which included superficial thrombophlebitis in the VTE cases and use of high hormone doses, reported the greatest increase in VTE risk for COC users compared to non-users.
- The increase in VTE risk for COC users compared to non-users has ranged between 2-fold and 10-fold.

Myocardial Infarction

- An increased risk for myocardial infarction has been attributed to COC use
- This risk is primarily observed in smokers aged 35 years or older, and in women with other underlying risk factors for coronary artery disease

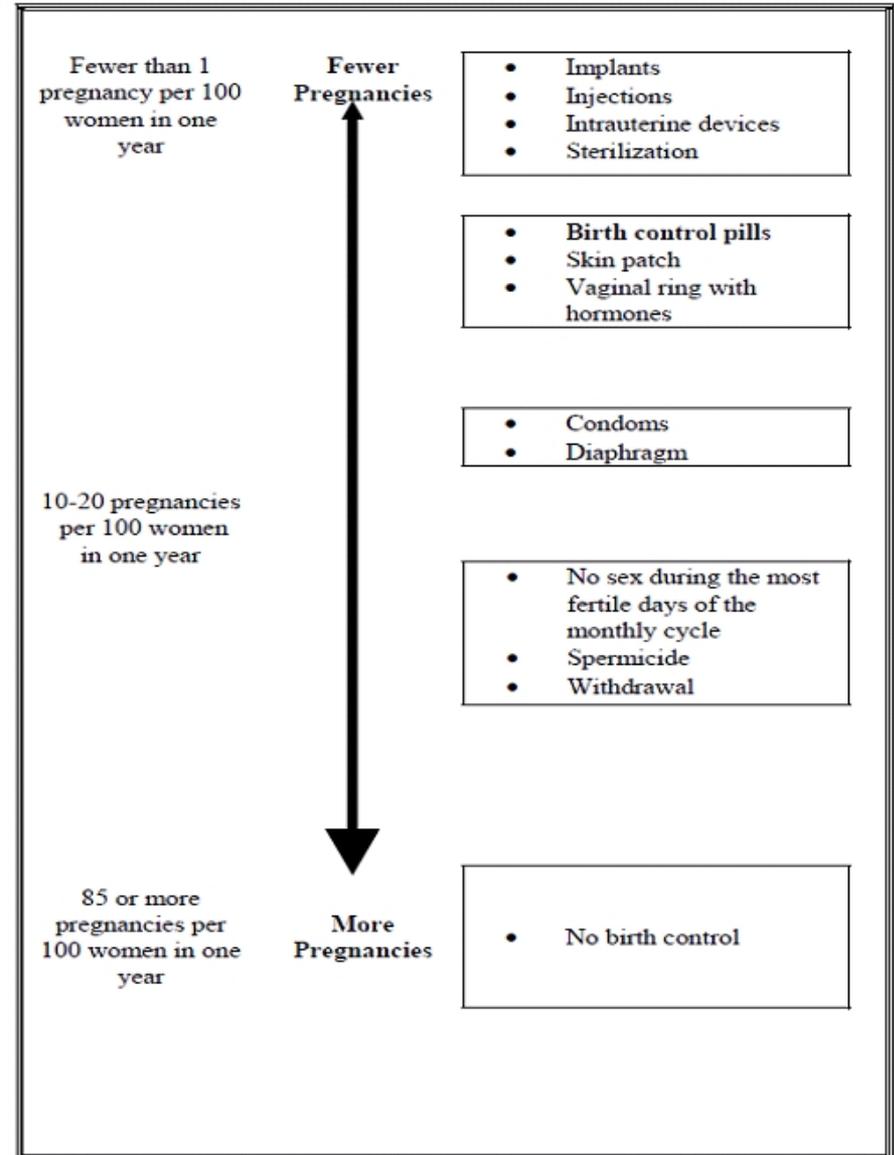
Risk of Stroke

- Mixed results (increase vs. no increase) are reported in the medical literature for both ischemic and hemorrhagic strokes
- Hypertension, smoking, and estrogen dose appear to be important factors

Efficacy Determination for COCs

- **Pearl Index:** Number of on-treatment pregnancies per 100 women-years exposure (usually in a 1-year clinical trial)
- Age 35 and younger
- Exclusion of cycles in which backup contraception was used
- The lower the Pearl Index, the more effective a contraceptive

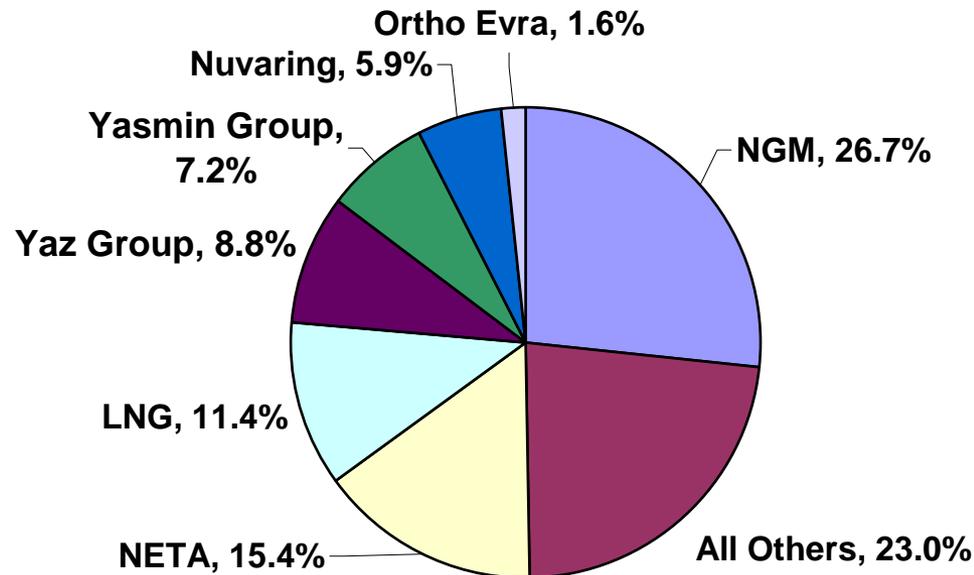
- The Pearl Index in most COC registration trials ranges from 0.5 to 3 pregnancies per 100 women-years
- The Pearl Index for Yasmin and YAZ are in the lower end of this range



Combined Hormonal Contraceptives Drug Utilization Total CHC Prescriptions Market (USC Class 33230, 33390) U.S. Outpatient Retail Setting, Year 2010

IMS, Vector One™: National VONA. Year 2002 to Year 2010. Data Extracted November 2011.

Share of CHC Market Prescriptions by Selected Groups, Year 2010





Yasmin Postmarketing Epidemiologic Studies - Interpretation

**Joint Meeting of the Advisory Committee for Reproductive Health Drugs
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**Rita Ouellet-Hellstrom, PhD, MPH
Associate Director for Science, Division of Epidemiology II
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Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research**

Preliminary Assessment

- Yasmin appears to be associated with a higher VTE risk than the CHC comparators in the more recent studies
- VTE **relative risks** for Yasmin vary by differences in
 - **Age, population characteristics & comparators**
 - VTE **relative risk** highest among young Yasmin users (age interaction) although the absolute risk increases with age
 - ATE **relative risk** may be higher among older Yasmin users
 - Risks differ based on comparator selected
 - **Exposure Definitions & Prescribing Trends**
 - Risk estimates differ when comparing All Users to New Users

Preliminary Assessment (continued)

- **Confounding**
 - Confounding variables selected or available for adjusting differ by study
 - Differences in risk estimates across studies may reflect these differences
- **Channeling**
 - Selective prescribing by providers more frequently associated with Yasmin
 - VTE risk is unknown among women with PCOS, acne, hirsutism & other gynecological disorders
 - Channeling with Yasmin may be an important contributor to increased VTE risks seen in more recent studies
- The contributions of these factors need to be evaluated before concluding that Yasmin carries a higher VTE risk than its comparators

Overview

- Age, Population Characteristics & Comparators
- Exposure Definitions & Use Trends
- Confounding: Adjustments & Covariates
- Channeling Evidence for CHC with drospirenone



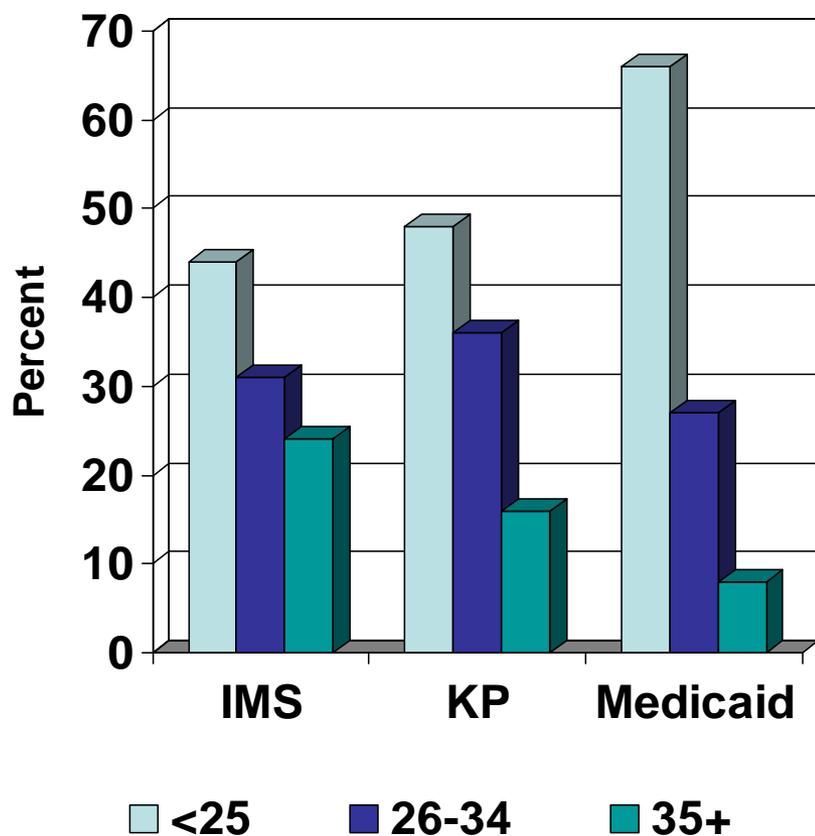
Age, Population Characteristics & Comparators

Is Mean Age Reflective of Other Population Characteristics?

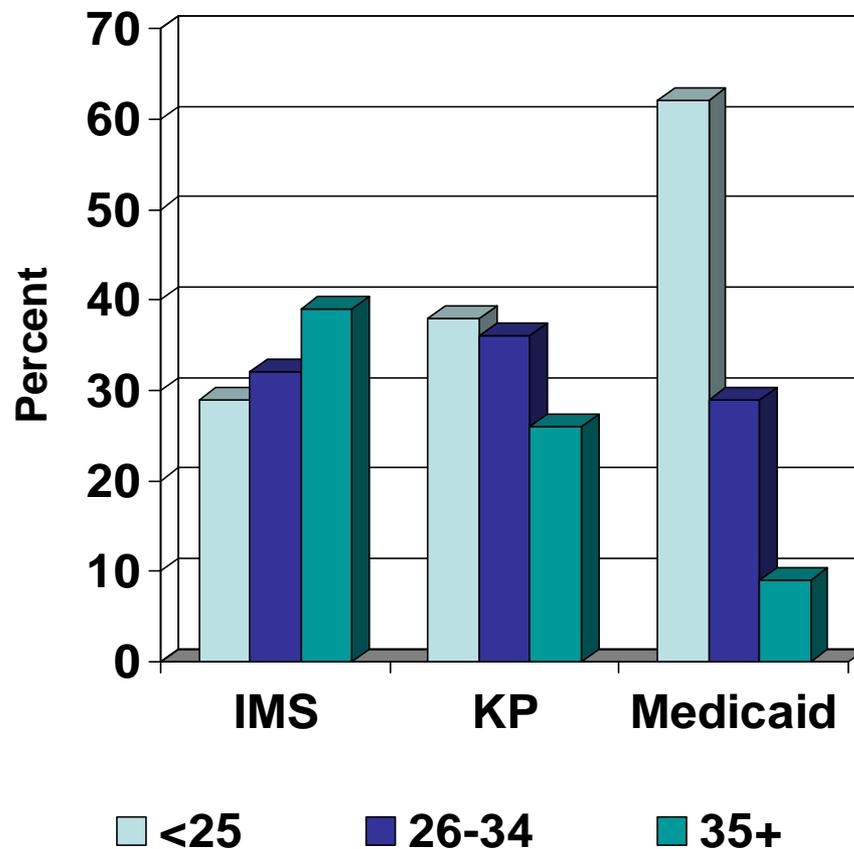
| Design | Authors | Age Range | Mean Age | | |
|--------------|----------------------|-----------|-------------------|-------------|--------------|
| Cohort | Dinger 2007 (EURAS) | All ages | Yasmin 26 | | |
| | | | LNG 25 | | |
| | | | Other 25 | | |
| Cohort | Lidegaard 2009, 2011 | 15-49 | Not provided | | |
| | | | Sidney (FDA) 2011 | Yasmin 26 | |
| | | | | LNG 28 | |
| Cohort | Sidney (FDA) 2011 | 10-55 | Other 27 | | |
| | | | Case-Control | Dinger 2010 | Not provided |
| | | | | | Jick 2011 |
| Case-Control | Parkin 2011 | 15-44 | Cases 32 | | |
| | | | Controls 32 | | |
| Case-Control | Vlieg 2009 | 18-50 | Cases 37 | | |
| | | | Controls 37 | | |

Age Distribution by CHC FDA Study

Yasmin Users



LNG Users



VTE Relative Risk Higher for Younger Yasmin New Users

| Comparator (Author) | Age group | Relative Risk | 95% CI | Comment |
|---|-----------|---------------|-----------------|-------------|
| Yasmin vs. LNG (Parkin 2011) | <35 | 3.7* | 1.3-10.7 | Interaction |
| | 35+ | 2.8* | 0.7-10.7 | |
| Yasmin vs. LNG2* (Sidney (FDA) 2011) | <35 | 2.2** | 1.3-3.5 | Interaction |
| | 35+ | 1.1** | 0.7-1.7 | |

* Estimated using the Odds Ratio; LNG's ethinyl estradiol dose not specified

** Estimated using the Hazard Ratio; Yasmin vs. levonorgestrel (LNG) with 30 µg ethinyl estradiol

ATE Relative Risk Higher for Yasmin New Users – FDA Study

| Yasmin vs. | Age group | Hazard Ratio | 95% CI | Comment |
|------------|-----------|--------------|----------------|-------------|
| COMP* | <35 | 0.6 | 0.2-2.3 | Interaction |
| | 35+ | 2.6 | 1.3-5.4 | |
| LNG2** | <35 | 0.5 | 0.1-2.1 | |
| | 35+ | 2.4 | 1.0-5.8 | |

* Includes levonorgestrel-, norgestimate-, and norethindrone acetate-containing CHC. This group also includes LNG

** Levonorgestrel-containing CHC with 30 µg ethinyl estradiol (EE) only

Incidence Rates Vary by Comparator & Study

| Author | Product | VTE | | ATE | | Mortality | |
|------------------------|---------|------|----------|------------|---------|------------|---------|
| | | IR* | 95% CI | IR* | 95% CI | IR* | 95% CI |
| Dinger 2007 (EURAS) | Yasmin | 9.1 | 5.9-13.3 | 0.7 | 0.1-2.5 | 1.4 | 0.4-3.6 |
| | Other | 9.2 | 7.2-11.5 | 2.1 | 1.3-3.4 | 2.0 | 1.2-3.2 |
| | LNG | 8.0 | 5.2-11.7 | 2.9 | 1.3-5.4 | 2.5 | 1.1-5.0 |
| Sidney 2011 (FDA) | Yasmin | 10.2 | -- | 1.1 | -- | 2.4 | -- |
| | COMP** | 6.0 | -- | 1.4 | -- | 3.5 | -- |
| | LNG2*** | 6.6 | -- | 1.6 | -- | 4.5 | -- |

* IR = Incidence Rates per 10,000 women-years

** COMP = includes levonorgestrel-, norgestimate-, and norethindrone acetate-containing CHC. This group also includes LNG

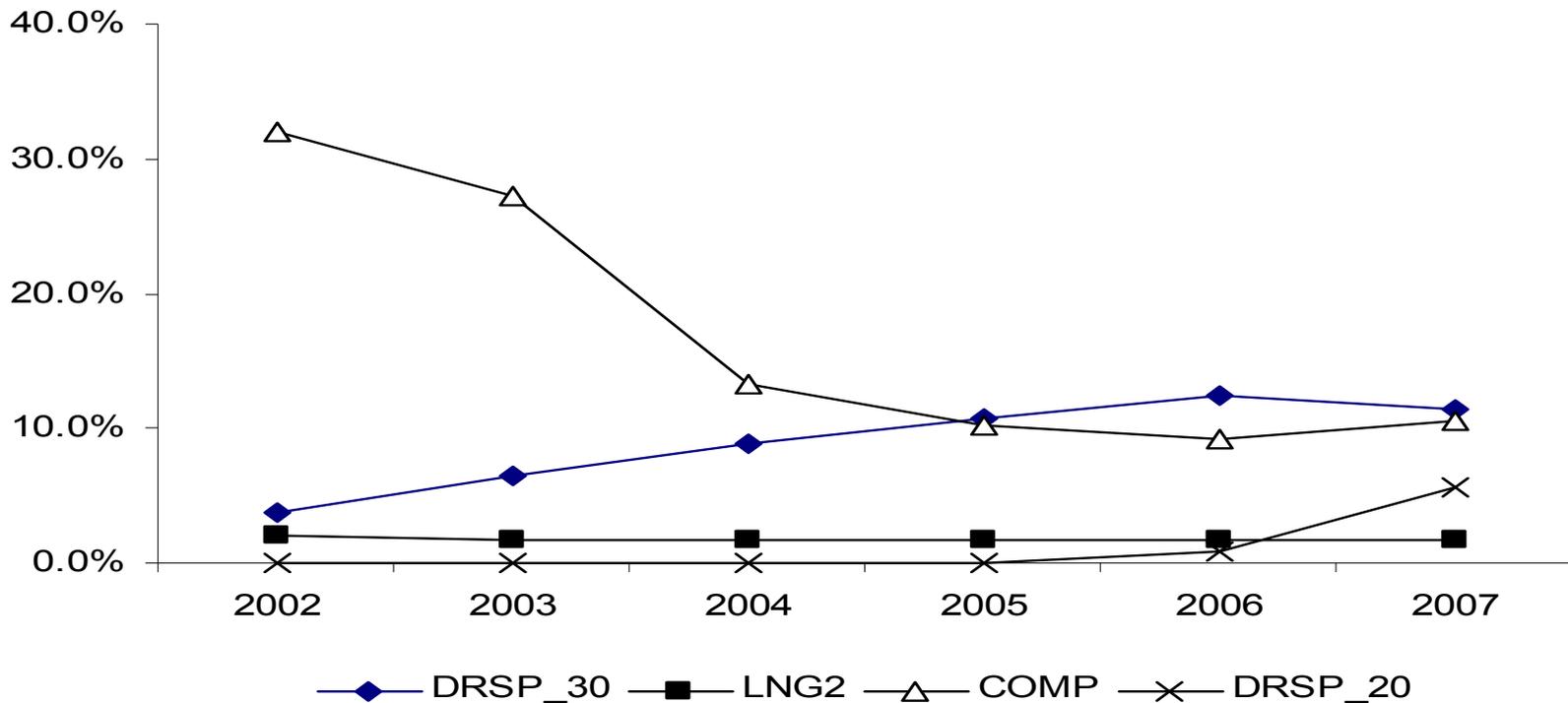
***LNG = levonorgestrel-containing CHC with 30 µg ethinyl estradiol (EE)



Prescription Trends & Exposure Definitions

Prescribing Trends Change Over Time for Some Study CHCs

Total Prescriptions as Proportion of the Total Market 2002-2007



Source: IMS Vector One®: National, Years 2002-2010 Data Extracted September 2011

DRSP_30 = Yasmin; DRSP_20 = Yaz; LNG = levonorgestrel-containing contraceptive; COMP = includes norgestimate-, norethindrone acetate- and levonorgestrel-containing contraceptives

Exposure Definitions Vary by Study

- Current use or initiation
 - EURAS, Lidegaard 2009, FDA 2011(all users), Vlieg 2009
- New User
 - excludes study CHCs in predefined prior months - Seeger 2007, Jick 2011
 - excludes all CHCs in predefined prior months
 - Parkin 2011, Lidegaard 2011, FDA 2011 (new users)

Adjusted VTE Rates Vary by Exposure Yasmin vs. LNG

| Author | Exposure | Hazard Ratio | 95% CI |
|-------------------|-----------|--------------|---------|
| Sidney 2011 (FDA) | All Users | 1.5 | 1.2-1.8 |
| | New Users | 1.6 | 1.1-2.2 |
| Lidegaard 2011* | All users | 2.0 | 1.6-2.4 |
| | New Users | 2.7 | 1.8-4.1 |

*Appendix 4: Rate ratio estimates (RR) of venous thromboembolism (VTE) between users of different combined oral contraceptives with 30-40 ug ethinyl estradiol (EE) according to different user categories for the whole period 2001-2009

Adjusted ATE Rates Vary by Exposure Yasmin vs. COMP*

| Author | Exposure | Hazard Ratio | 95% CI |
|----------------------|-----------|--------------|----------------|
| Sidney 2011 (FDA) | All Users | 1.0 | 0.6-1.7 |
| | New Users | 2.1 | 1.1-3.8 |

* COMP Includes levonorgestrel-, norgestimate- and norethindrone acetate-containing CHCs



Confounding

Covariates for Matching or Adjustments

- All studies
 - Age (adjusted or matched)
 - Calendar time or index date
- Some studies
 - Site, general practice, region (Sidney, Jick, Parkin, Vlieg)
 - Education, duration of current use (Lidegaard)
 - “10% rule” (covariates included if risk estimate changed by $\geq 10\%$)
 - FDA 2011, Jick 2011 (no covariate satisfied criteria so none included)
- Important confounders obtained from personal interviews (Dinger 2007, 2010, Vlieg 2009)
 - Personal & family history of VTE, lifetime CHC use, BMI, smoking (current & ever use), other medications & other chronic diseases

Measured Covariates Included in Propensity Score - Seeger 2007

- Selection based on
 - “Expected associations with Yasmin”
 - “Known characteristics predicting risk between Yasmin & other oral contraceptives”
- List of covariates (varied over time)
 - Age, enrollment & plan, time, region, health care utilization
 - Laboratory tests & procedures
 - Clinical diagnoses
 - Other medications

Effects of Adjustment

- When both are provided, adjusted estimates are either lower or the same as unadjusted rates for VTE when using the same comparator in the same population - Jick 2011
 - OR_{unadj} 3.2 (95% CI: 1.5 to 7.0)
 - OR_{adj} 3.3 (95% CI: 1.4 to 7.6)
- Greater differences in risk estimates are seen across studies
 - Covariates used for adjustment within a study appear not to change the risk estimate significantly

Does VTE Risk Change with Tighter Adjustment? - Yasmin vs. LNG

| Author | Hazard Ratio | 95% CI | Adjusted Covariates |
|------------------------|--------------|---------|---|
| Lidegaard 2011 | 2.0 | 1.6-2.4 | Age, calendar year, education & length of use |
| Sidney 2011 FDA | 1.5 | 1.2-1.8 | Age, site, calendar time |
| Dinger 2007 EURAS | 1.0 | 0.6-1.8 | Age, BMI, family history of VTE, smoking, etc |
| Seeger 2007 i3 Ingenix | 0.9 | 0.5-1.6 | Propensity Scores |



Evidence of Channeling Greater for Yasmin

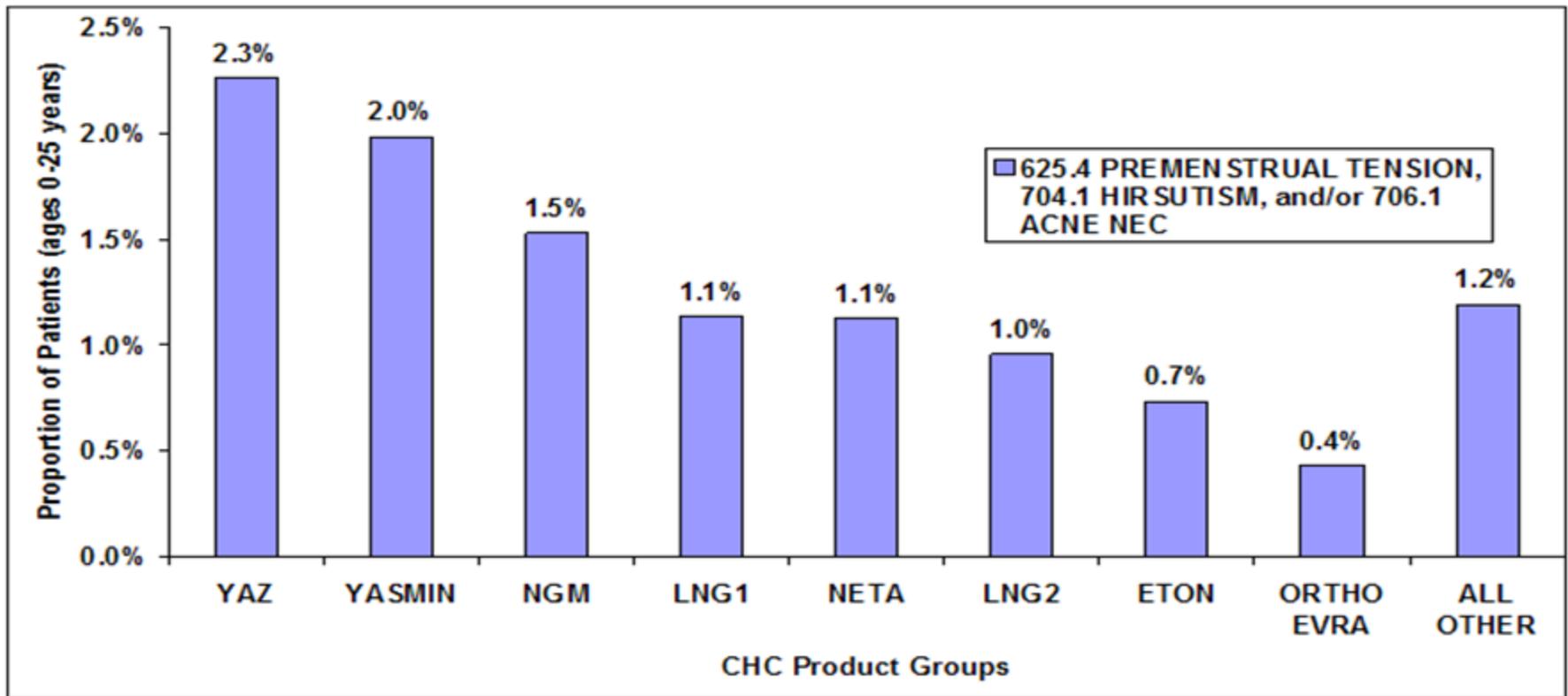
Non-Contraceptive Uses of CHCs

- Directed prescribing towards or away from women with co-morbid health conditions evident for Yasmin
- Use of Yasmin associated with women who have codes for
 - Menstrual cycle problems: dysmenorrhea, menorrhagia
 - Polycystic Ovary Syndrome (PCOS) & associated symptoms: acne, hirsutism, alopecia
- Drospirenone reported to improve acne & hirsutism
- Adjusting for some gynecological disorders (e.g. menstrual cycle disorders, inflammation of pelvic area) appears to lower VTE risks
- But so what? Are these women at increased risk for VTE?
 - Sparse information in the literature

Other Measured Covariates Suggesting Channeling - FDA Study

| Covariate | Products | All ages (%) | < 35 years (%) | 35+ years (%) |
|-----------|------------|--------------|----------------|---------------|
| Acne | Yasmin | 4.2 | 4.6 | 1.9 |
| | Comparator | 2.1 | 2.5 | 0.8 |

Associated Codes for Acne, Hirsutism, Premenstrual Tension by CHCs US women Age < 26 years (2007-2010)



Source: Wolters Kluwer Health Concurrent Product Analyzer. Years 2007 – 2010. Extracted October 2011

Selected Diagnoses Associated with CHC Use As Reported by Office-Based Physician Practices 2001-2007 Age < 26 Years

| | Yasmin% | NGM % | LNG2 % |
|--------------|----------|-------|--------|
| Dysmenorrhea | 5 | 5 | 8 |
| Acne | 2 | 5 | 0 |
| PCOS | 2 | 0 | 0 |

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Thank You



Yasmin Postmarketing Epidemiologic Studies - Overview

**Joint Meeting of the Advisory Committee for Reproductive Health
Drugs and the Drug Safety and Risk Management Advisory Committee
December 8, 2011**

Rita Ouellet-Hellstrom, PhD, MPH
Associate Director for Science, Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Overview

- Yasmin Passive Surveillance Findings
 - Adverse Event Reporting System (AERS) Case Summary
 - Drug Utilization Review
 - Reporting Rates
- Post Approval & Other Epidemiologic Studies
 - EURAS (Dinger 2007)
 - i3 Ingenix (Seeger 2007)
 - Others 2009-2011
- Post Approval Study Results
- CHC Product Utilization Trends
- FDA-funded Study
 - Unresolved Questions
 - Study Rationale

Passive Surveillance for Yasmin

Summary of AERS Cases & Reporting Rates

- Comparisons of Yasmin reporting & drug use to those of older combined hormonal contraceptives (CHCs) showed
 - Older Yasmin users
 - More off-label use (e.g., menstrual cycle control, cysts, polycystic ovary syndrome, migraine...)
 - Initially, more than 50% of reports were for women outside the US
- Yasmin thrombotic & thromboembolic reporting rates were
 - Similar for VTE events
 - Slightly higher for arterial events (ATE) including strokes
 - Higher for deaths



Post Approval & Recent Epidemiologic Studies

Post Approval Epidemiologic Studies

Overall Study Design

- European Active Surveillance Study (EURAS) - Dinger 2007
 - European prescribers recruited women who received a new CHC prescription
 - All users who signed an informed consent were enrolled
 - Personal or mail interviews at baseline and every 6 months

- i3 Ingenix US Study - Seeger 2007
 - Yasmin & other CHC initiators identified in the United HealthCare (UHC) database
 - Yasmin initiators matched on propensity scores (PS) to 2 other CHC initiators quarterly
 - PS scores based on clinical information in the 6 months prior to CHC initiation
 - 98% Yasmin initiators (22,429) matched, 458 (2%) not matched

Recent Epidemiologic Studies

- Population cohort study using Danish registries – Lidegaard 2009
- Population-based case-control study from six coagulation clinics in Netherlands – Vlieg 2009
- Community-based case-control study in Germany – Dinger 2010
- Case-control study in US-based PharMetrics database – Jick 2011
- Case-control study in the UK GPRD database – Parkin 2011
- Re-analysis of the population cohort study using Danish registries – Lidegaard 2011

Studies Discussed Today

Focus Mainly on Yasmin

- Yasmin
 - 3 mg drospirenone (DRSP)-containing hormonal contraceptive with 30 μ g ethinyl estradiol (EE)
- YAZ
 - 3 mg DRSP with 20 μ g EE not considered except in Lidegaard's 2011 paper & drug use trends

Studies Showing NO Increased VTE Risk

| Author | Design | Population Source | Reference Group | Relative Risk | 95% CI* |
|-----------------------------|--------------------|--|-----------------------------|---------------|---------|
| Seeger 2007 (i3 Ingenix) | Cohort prospective | United HealthCare Database | Yasmin vs. Other | 0.9** | 0.5-1.6 |
| Dinger 2007 (EURAS) | Cohort prospective | Practitioner Referrals | Yasmin vs. LNG | 0.9* | 0.5-1.4 |
| | | | Yasmin vs. Other | 0.8* | 0.5-1.2 |
| Dinger 2010 | Case-control | Practitioner Referrals Community controls | Yasmin [†] vs. LNG | 1.0** | 0.5-1.8 |

•CI = confidence interval;

** Thromboembolism estimated using hazard ratio

*** VTE risk estimated using odds ratio

† Drospirenone-containing CHC with 30µg EE. Includes Yasmin but may also include generics

Studies Showing an Increased VTE Risk Compared to Non-Users (NU)

| Author | Design | Population Source | Comparison Group | Relative Risk | 95% CI |
|----------------|----------------------|---------------------|---------------------|------------------|----------|
| Lidegaard 2009 | Cohort retrospective | Danish Registries | LNG vs. NU | 2.0* | 1.8-2.3 |
| | | | DRSP vs. NU | 4.0* | 3.3-4.9 |
| Vlieg 2009 | Case-control | Clinics + community | LNG vs. NU | 3.6 [†] | 2.9-4.6 |
| | | | DRSP vs. NU | 6.3 [†] | 2.9-13.7 |
| Lidegaard 2011 | Cohort retrospective | Danish Registries | LNG 30ug EE vs. NU | 2.2 [‡] | 1.7-2.8 |
| | | | DRSP 30ug EE vs. NU | 4.5 [‡] | 3.9-5.1 |

* Adjusted for age, calendar year & education; DRSP /LNG ratio ~2.0

[†] VTE risk estimated using odds ratios (OR); DRSP/LNG ratio ~ 1.8; [‡] DRSP/LNG ratio ~ 2.0

Studies Showing an Increased VTE Risk Compared to LNG*

| Author | Design | Population Source | Comparison Group | Relative Risk | 95% CI*** |
|-------------|--------------|-------------------|------------------|---------------|-----------|
| Jick 2011 | Case-control | PharMetrics | DRSP vs. LNG | 2.4** | 1.7-3.4 |
| Parkin 2011 | Case-control | GPRD | DRSP vs. LNG | 3.3† | 1.4-7.6 |

* LNG= levonorgestrel-containing combined oral contraceptive; **Risk estimated using Odds Ratio (OR); Adjusted for duration & matched on age and index year; ***CI = confidence interval

† Risk estimated using Odds Ratio (OR); Adjusted for body mass index & matched on age & index year;



CHC Product Utilization Trends in the US 2002-2010



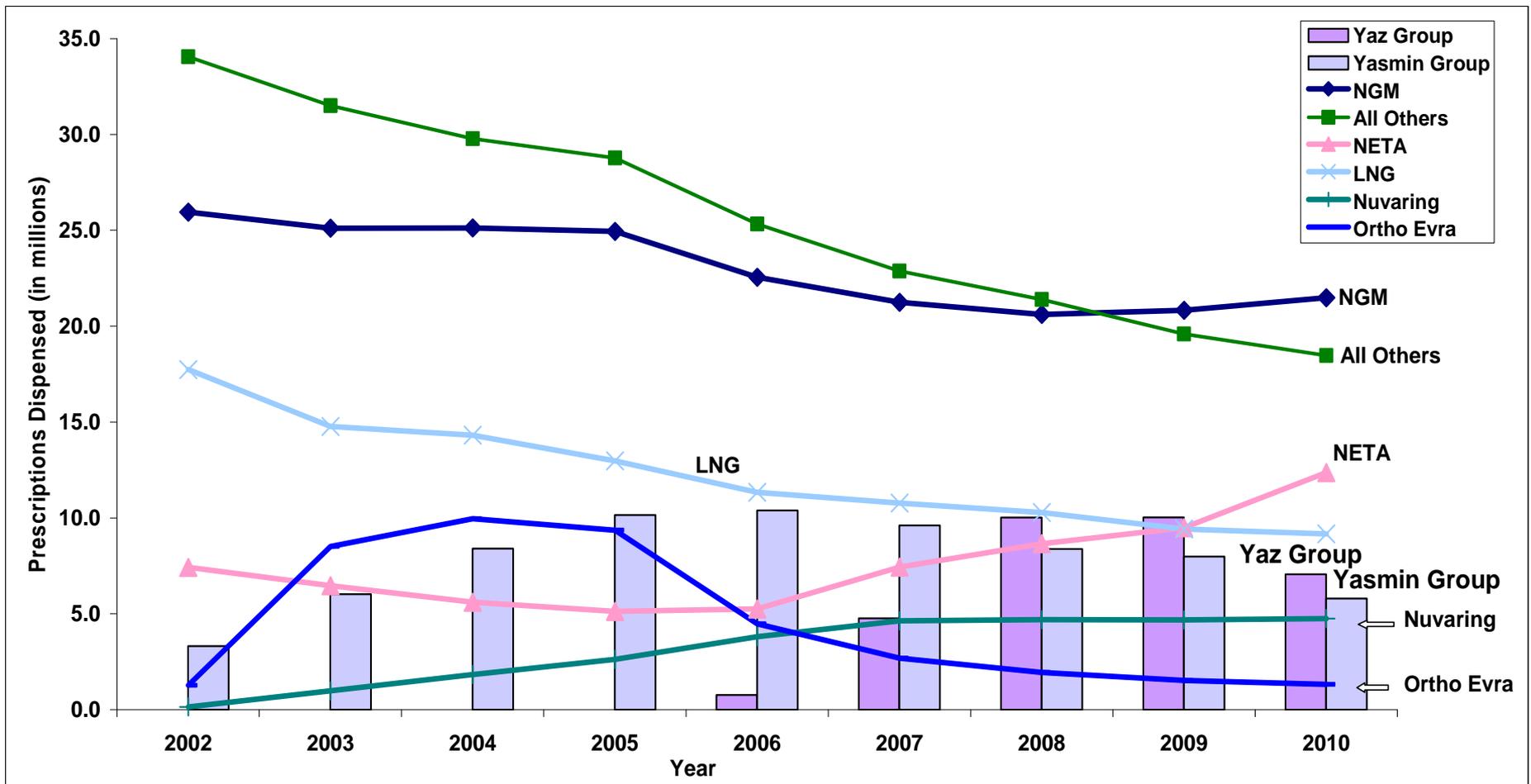
Combined Hormonal Contraceptives Drug Utilization

Total CHC Prescriptions Market (USC Class 33230, 33390)

U.S. Outpatient Retail Setting, Years 2002-2010

IMS, Vector One™: National VONA. Year 2002 to Year 2010. Data Extracted November 2011.

Estimated Number of Prescriptions Dispensed for CHC Products by Selected Product Groups



Rationale for Initiating FDA-Funded Study

- The post approval epidemiologic studies
 - Evaluated 1 product (Yasmin) compared to LNG-containing & other CHCs
 - Identified cardiovascular deaths only
 - Provided limited evaluation of Yasmin's risk in US populations

Rationale for Initiating FDA-Funded Study

- Unresolved questions included the need to evaluate risk
 - In **All newly** approved CHCs (prior to 2008)
 - In **All deaths** including sudden deaths
 - In a more **expanded age** group (10 to 55 years)
 - In other US insured groups (e.g., Medicaid)
 - By product use & prescribing patterns

FDA-Funded Study

- FDA study was initiated in 2008
- Report posted on FDA's website October 2011
 - <http://www.fda.gov/Drugs/DrugSafety/ucm277346.htm>
- Detailed discussion of all epidemiologic studies noted will follow Dr. Sidney's presentation



Thank You



Risk/Benefit Analysis Summary for Drospirenone-containing Oral Contraceptives

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Summary of Efficacy

- Acceptable Pearl Index for DRSP-containing COCs – on the order of 1-2 pregnancies per 100 women-years
- Secondary indications include acne, PMDD, and to raise folate levels
 - Not all DRSP products have all of these secondary indications
 - Approved based on submission and review of clinical data

Initial Signals of Potential Concern

- Early adverse event reporting suggested higher reporting rates of death and ATEs
- Initial post-approval epidemiologic studies provided reassurance that risk of VTE was not increased for DRSP products
- Subsequent publications and the FDA-funded study have generally reported an increased VTE risk for DRSP users compared to users of COCs with other progestins
- Almost all studies evaluated ONLY Yasmin

Factors that May Influence Risk Estimates

- Different claims databases
- Evaluation of All Users vs. New Users
- Inability to evaluate potential confounders
 - Known but unmeasured confounders
 - Unknown confounders
- “Channeling” or selective prescribing

Preliminary FDA Assessment

- Yasmin appears to be associated with an increased risk of VTE compared to COCs with other progestins
- However, many factors influence these risk estimates
- Need to evaluate impact of these factors in future studies or re-analyses of existing data before we can conclude that Yasmin carries an increased risk of VTE

Issues for Committee Discussion

- What is the impact of differences in study population, comparators, exposure definitions, handling of confounding, and possibly channeling bias on one's ability to compare study results?
- Should some of the studies or findings be given greater weight than others?
- Are users of DRSP-containing COCs at an increased risk of VTE compared to users of COCs containing other studied progestins?
- Do the benefits of DRSP-containing COCs for prevention of pregnancy outweigh the risks? If not, are there subpopulations for whom the risk/benefit profile would be favorable?
- Does current labeling adequately reflect the risk/benefit profile of DRSP-containing COCs?