U.S. FOOD & DRUG ADMINISTRATION

New Drug Application 204017
AG200-15 transdermal system
(120 mcg levonorgestrel/ 30 mcg ethinyl estradiol)

Opening Remarks
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 30, 2019

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Office of New Drugs, Center for Drug Evaluation and Research
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Purpose

The Division is seeking advisory committee input on:

- Acceptability of the effectiveness and safety profile of AG200-15
- Assessment of the benefit/risk

AG200-15

Features

- 28 cm^2 matrix type transdermal system (TDS)
- Contains levonorgestrel (LNG) and ethinyl estradiol (EE)
- Delivers 120 mcg LNG and 30 mcg EE daily

Dosing regimen

- One TDS to be worn for 7 days for three consecutive weeks
- One TDS-free week
- TDS may be applied to the abdomen, buttock, or upper torso

Proposed indication

- Prevention of pregnancy in females of reproductive potential
- Limitation of use statement related to body mass index (BMI) and weight

Combined Hormonal Contraceptive (CHC) Development

Since the first CHC approval, the priority has been to develop:

- Lower hormonal dose formulations
- More convenient dosing regimens and dosage forms

Effectiveness of the CHC to prevent pregnancy must outweigh the safety risks for approval.

CHC Development

A January 2007 advisory committee (AC) discussed topics including:

- Study design and methods for hormonal contraceptive trials
- Assessment of the benefit/risk for hormonal contraceptives

CHC Development

2007 AC recommendations on benefit/risk for CHCs:

- Allow flexibility in Pearl Index point estimates and upper bounds of confidence intervals for new applications
- Allow a variety of effective and safe products
- Consider active-controlled trials

CHC Development

2007 AC concerns regarding active-controlled trials:

- Permitting comparison with another hormonal product could lead to a progressive widening in acceptable efficacy values (“creep”) and less decipherable results
- Feasibility of conducting active controlled trials may be a barrier to introduction of new agents

Division's Perspective on CHC Development (2019)

For CHC trials:

- Evaluation of each CHC product on its own benefit/risk assessment
- Inclusion of adolescents, women with higher BMIs, under-represented minorities, and other subpopulations
- On-treatment pregnancies limited to those in which conception occurred during the treatment cycle
- Standardized data collection of bleeding and spotting
- Open-label, single-arm trial(s) of at least one year in duration as the basis of effectiveness and safety determination

Division's Perspective on CHC Development

For CHCs as a class, the Division reviews information including, but not limited to:

- Pregnancy rates
- Adverse events (AEs) of special interest
- Tolerability and usability

How To Assess CHC Effectiveness

- Pearl Index is the primary efficacy endpoint defined as the number of pregnancies per 100 women-years of use.
- CHC effectiveness is defined by the upper bound of the 95% Confidence Interval (UB 95% CI) of the Pearl Index
- The Division's criteria for CHCs effectiveness is based on:
  - Pooled national survey data
  - Historical CHC trial data
  - Finding a favorable benefit-risk
- Unmet medical need: a condition whose treatment or diagnosis is not addressed adequately by available therapy

Division's Current Thinking on AG200-15

Benefits:

- Unintended pregnancy is a significant public health problem
- From a pharmacokinetic standpoint, AG200-15 delivers a lower dose of EE as compared to the currently approved TDS contraceptive
- Another transdermal CHC could provide an additional alternative for women seeking a non-invasive method of contraception
- AG200-15 reduces the risk of pregnancy compared to women not using contraception

Division's Current Thinking on AG200-15

Division's Considerations:

- AG200-15 does not meet FDA's regulatory definition of unmet need
- Does not represent a "low dose" product given the availability of 10-20 mcg ethinyl estradiol (EE) CHCs
- AG200-15 does not convey any safety advantage over other types of CHCs
- Pearl Index raises effectiveness concerns
- VTE incidence rate raises a safety concern
- Tolerability (e.g. cycle control) raises clinical use concerns

We are seeking input from the Advisory Committee before reaching a final decision on approvability of this product.

Discussion and Voting Questions

Discussion Question 1

1. Discuss the effectiveness of AG200-15, including:
    a. Interpretation of efficacy results from Study 23 as they related to study design and enrolled patient population
    b. Interpretation of subgroup analyses by body mass index, weight, and race/ethnicity

Discussion Question 2

2. Discuss the safety profile of AG200-15, including:
    a. Interpretation of the venous thromboembolism (VTE) safety signal
    b. Interpretation of product tolerability data (e.g., cycle control)

Voting Question

3. Do the benefits of AG200-15 outweigh its risks and support approval for the prevention of pregnancy?

   If you vote YES, explain the rationale for your vote and address the following:

   - Whether this product should be approved for use in the general population or in a narrower patient population
   - How this product should be used within the context of available contraceptive therapies

   If you vote NO, explain the rationale for your vote and provide any recommendations.


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Background
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 30, 2019

Jerry Willett, M.D.
Clinical Team Leader, Division of Bone, Reproductive and Urologic Products
Office of New Drugs, Center for Drug Evaluation and Research
Food and Drug Administration

Overview

- Unintended pregnancy
- Combined hormonal contraceptive (CHC) development in the U.S.
- Regulatory history of AG 200-15
- Trial considerations for AG 200-15

Unintended Pregnancy

- CDC definition: pregnancy that is unwanted or mistimed
- In 2011, 45% of the 6.1 million pregnancies in the U.S. were unintended
- Public health consequences include adverse maternal and child health outcomes as well as social and economic costs

CHC Development in the U.S.

A delicate balance

- Prevent unintended pregnancies with highly effective products
- Reduce serious adverse reactions:
  - Death
  - Venous thromboembolism events (VTEs)
  - Myocardial infarction (MI)
  - Stroke
- Reduce tolerability issues such as unscheduled bleeding that may discourage use or result in discontinuation

CHC Development

Study design changes

- More accurate and frequent pregnancy testing during trial(s)
- Better imaging to estimate conception date
- Focus on overall pregnancy rate rather than method or user failure analyses
- Exclusion from effectiveness evaluation of treatment cycles in which concurrent contraception was used or no sexual activity was reported
- Electronic diary to record study drug use and cycle control

CHC Development

Study population

- U.S./Canada - reflective of current demographics
- Sexually active, regular menstrual cycles, no known infertility issues for the partners
- Age up to 35 years for effectiveness; all patients for safety
- Adequate washout of other hormonal contraceptives; no concurrent contraceptives
- Encourage enrollment of obese subjects and adolescents

Obesity

- Obesity prevalence in U.S. adults increased to 40% in 2015-2016 (10% increase in approximately 15 years)
- Obesity prevalence in reproductive age women in U.S. age 20-39 in 2015-2016 was 37%

National Center for Health Statistics – CDC October 2017

Obesity/ CHC Development

- Obese subjects largely excluded from pre-approval clinical trials of CHCs
- Some applicants have allowed BMI greater than 30 kg/m^2 in trials
- Mixed results when evaluating BMI and CHC effectiveness

BMI and Contraceptive Effectiveness

FDA meta-analysis (Yamazaki et al. *Contraception* 92:445-52)

- Meta-analysis of seven clinical trials of oral CHCs
- Objective: evaluate the impact of obesity on contraceptive effectiveness
- Only 2 products had a large number of cycles (>4,000) in obese subjects

Limitations

- Differences between non-obese and obese may not be clinically meaningful
- Possibility of selection bias/lack of compliance information

Conclusion: Although obese subjects may have slightly higher Pearl Index, more data on obese women is necessary to allow further evaluation.

AG200-15 Regulatory History

Regulatory: First Review Cycle

- Application for AG200-15 originally submitted to the Division in April 2012
- Efficacy and safety focused on two phase 3 studies (Studies 12 and 13)
- The Division's non-approval in February 2013 stated Studies 12 and 13 had unacceptable on-treatment pregnancy rates and significant problems with study conduct and product quality. The Division informed the Applicant that a new phase 3 trial would be required.
- At the October 2013 end-of-review meeting, the Division informed the Applicant that no combination hormonal contraceptive had been approved with an upper bound of the 95% confidence interval around the Pearl Index that exceeded 5.

Regulatory: Second Review Cycle

- Applicant's NDA for AG200-15 was resubmitted in June 2017 with clinical data from a new phase 3 study (Study 23).
- The Division did not approve the AG200-15 resubmission in 2017. There were continuing concerns about the unacceptable pregnancy rate, product adhesion, high subject withdrawal rates, and manufacturing quality issues.
- The Division will focus primarily on clinical data from Study 23 for this Advisory Committee Meeting.

Regulatory: Third Review Cycle (Current)*

- The Applicant filed a resubmission in May 2019 with additional product quality data from an in-house comparative adhesion study.
- No new efficacy data was submitted.

*Of note, between the second and third review cycles, there were appeals submitted by the Applicant (summer 2018)

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Trial considerations for AG200-15

CHC Development – AG200-15

Factors that may increase pregnancy rates in current clinical trials of CHCs:

- Dosing Considerations: Decreasing hormone doses/less margin for missing product
- Trial Conduct Considerations:
  - More sensitive and more frequent pregnancy testing
  - Inclusion of obese subjects
- Compliance: Higher noncompliance of subjects in U.S. trials compared to Europe

Dosing Considerations – AG200-15

- In 1996, 2.5% of all oral CHC prescriptions in the U.S. were for formulations with 50 mcg of estrogen (Lobo and Mishell, 1997)
- There is now an approved oral CHC containing just 10 mcg of ethinyl estradiol

Applicant's Study 14 compared ethinyl estradiol (EE) in AG200-15 versus that in a oral CHC containing 35 mcg of EE. The Division's analysis of pharmacokinetic data found similar EE steady-state systemic exposure (area under curve) for both products.

AG200-15 is not a low dose EE CHC product

Trial Conduct Considerations – AG200-15

- Pregnancy testing requirements have generally been consistent over the last ten years
- The Division has been consistent in its recommendation to exclude cycles without at least one episode of vaginal intercourse for other products in development in the last ten years.
- Although Study 23 had a greater proportion of obese subjects, its overall design and conduct were similar to other recent phase 3 contraceptive trials.

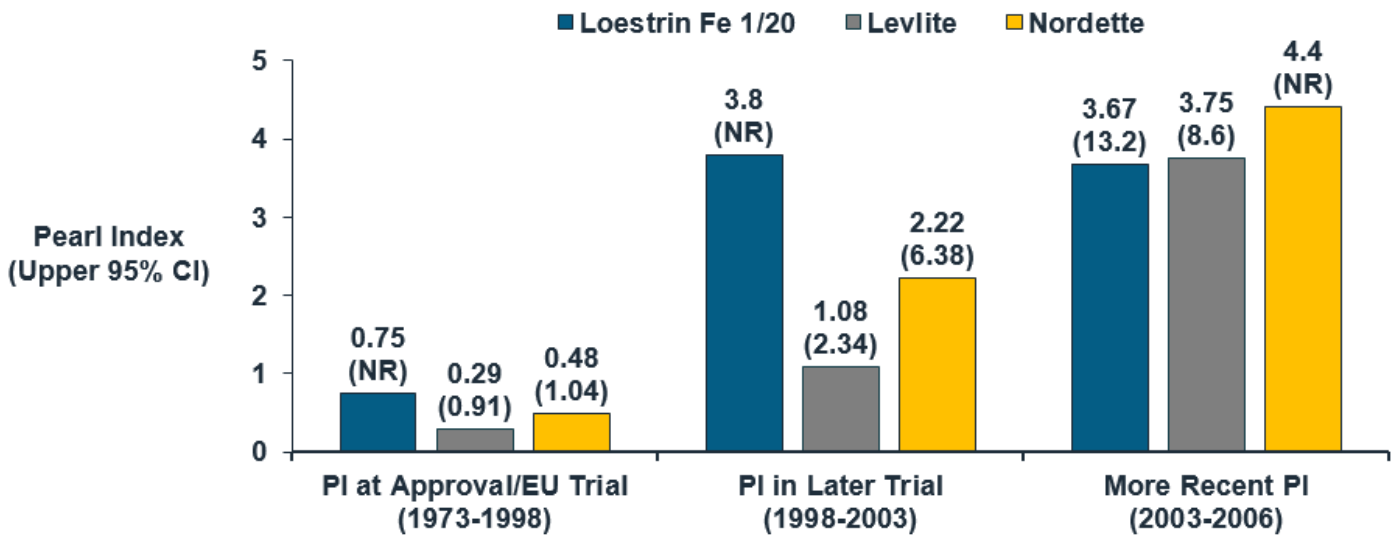
Other Considerations – AG200-15

Study 23 strongly encouraged compliance. Subjects were required to have 90% compliance with electronic diary during run-in period. Compliance was reviewed at all office visits and phone contacts (essentially for all treatment cycles).

- Pregnancy rates in clinical trials are usually lower than postapproval rates, especially for contraceptive products requiring user compliance.
- Products that derive effectiveness from clinical trial(s) with strict compliance during clinical studies may have increased pregnancy rates postapproval.

In addition, there is uncertainty about effectiveness of products and the postapproval pregnancy rates when there are subjects lost to follow-up and/or prematurely discontinuing without an exit pregnancy test.

Pearl Indices of Approved CHCs

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Effectiveness Considerations
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 30, 2019

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Office of Biostatistics, Center for Drug Evaluation and Research
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Outline

- Study design considerations for combined hormonal contraceptives (CHCs)
- Evaluation of AG200-15 effectiveness per Study 23
  - Overview of Study Design
  - Efficacy Results
  - Summary

Study Design Considerations For CHCs

Design Considerations

Phase 3 trial(s)

- Open-label, single-arm, at least one year in duration

Primary efficacy endpoint: Pregnancy rate measured by Pearl Index in women ≤35 years old

Pearl Index: # of pregnancies per 100 woman-years of product use

$$\text{Pearl Index} = \frac{\#\ of\ on{-}treatment\ pregnancies\ X\ 13\ cycles}{\#\ of\ evaluable\ cycles} \text{ x } 100$$

- On-treatment pregnancies: those that occur during product use or within a specific timeframe after last use of the product.
- Evaluable cycles: on-treatment cycles where vaginal intercourse occurs and no back-up or emergency contraception is used.

Design Considerations

Study Size

- **NME**: at least 20,000 cycles and 400 completers
- **Non-NME**: at least 10,000 cycles and 200 completers

Subgroup Analyses

- Body mass index (< 30 or ≥ 30 kg/m^2), race, ethnicity, and region (US/Canada or rest of world)

NME: new molecular entity

Primary Efficacy Assessment

- **Upper bound of 95% confidence interval (CI) for Pearl Index ≤ 5 for CHCs**
- **Rationale for 5 as the effectiveness criteria**
  - National surveys: 5%-7% of women experience unintended pregnancy during first year of typical use of hormonal pills (Trussell & Kowal, 1998; Trussell & Aiken, 2018)
  - Upper bound of the 95% CI for approved CHCs is ≤ 5
  - Serious safety risks of arterial thrombotic and venous thromboembolic events (ATEs and VTEs)
- **Limitations of 5 as the effectiveness criteria**
  - Survey results
  - Limitations of cross-study comparisons

Applicant was informed that the Division had never approved a CHC for which the upper bound exceeded 5 (October 10, 2013 Meeting Minutes).

Evaluation of AG200-15 Effectiveness Per Study 23

Trial Design for Study 23

- Single arm, open label, multicenter, one year (thirteen 28-day cycles)
- 102 U.S. clinical sites
- 2,032 enrolled women, aged 18 to 40 years, no body mass index (BMI) or weight restrictions
- Key enrollment criteria: ≥ 90% compliance with electronic diary entry and returned two check-in phone calls during the two-week run-in period

Trial Design for Study 23

"The Study is sized to provide 90% power to establish that if the underlying Pearl Index is no larger than 3.5, the Pearl Index will have an upper limit of a two-sided 95% confidence interval no larger than 5." (Statistical Analysis Plan, 2016, page 9-10)

The evaluable cycles in Study 23 exceeded the number of recommended cycles for the primary assessment.

Primary Analysis Population (N = 1,736)

- Age ≤ 35 years
- Wore at least one AG200-15 TDS during the study
- Negative serum pregnancy test at enrollment
- At least one evaluable cycle

Pre-Specified Primary Endpoint

Pearl Index in women ≤ 35 years old

- **On-treatment pregnancy**: pregnancy with estimated date of conception between the date of first AG200-15 application and 7 days after removal of last AG200-15 system
- **Evaluable cycle**: all complete or incomplete on-treatment cycles in which vaginal intercourse occurred and no back-up contraception was used

Secondary Endpoints

Pearl Index in subgroups of women ≤ 35 years old

Pre-specified

- BMI (< 30 or ≥ 30 kg/m^2)
- Race (Black, White, Other)
- Ethnicity (Hispanic or Latino or not Hispanic or Latino)

Not pre-specified

- Weight (< 92 kg or ≥ 92 kg)

Primary Analysis: Pearl Index in Women ≤ 35 Years

N	# On-Treatment Pregnancies	# Evaluable Cycles	Pearl Index	95% CI
1,736	68	15,165	5.8	(4.5, 7.2)

For the overall population, both the point estimate of Pearl Index and the upper bound of its 95% CI exceed 5.

Subgroup Analyses by BMI and Weight

Population	N	# On-Treatment Pregnancies	# Evaluable Cycles	Pearl Index (95% CI)
BMI (kg/m^2)*				
Non-obese (< 30)	1,123	33	9,888	4.3 (2.9, 5.8)
Obese (≥ 30)	612	35	5,264	8.6 (5.8, 11.5)
Weight (kg)				
< 92	1,402	46	12,276	4.9 (3.5, 6.3)
≥ 92	334	22	2,889	9.9 (5.8, 14.0)

*One subject in the primary analysis population does not have BMI information.

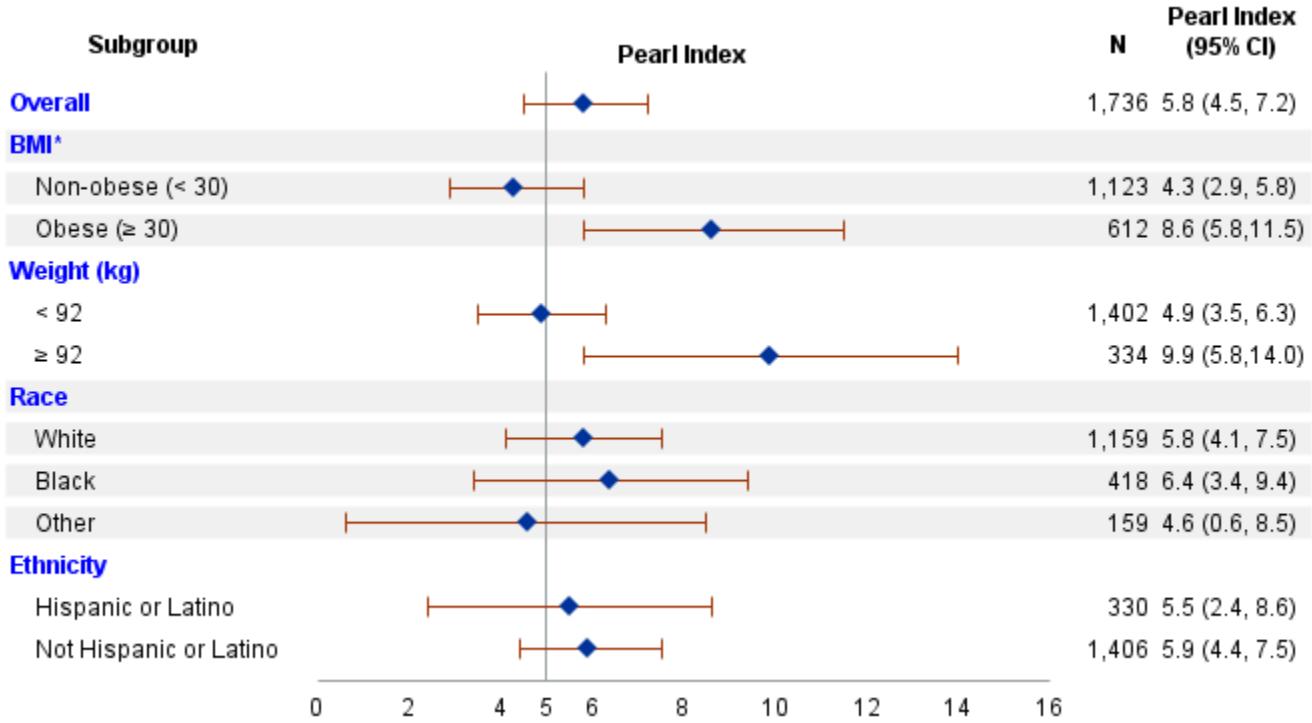
Analyses in women ≤ 35 years

Subgroup Analyses by Race and Ethnicity

Population	N	# On-Treatment Pregnancies	# Evaluable Cycles	Pearl Index (95% CI)
Race				
White	1,159	46	10,281	5.8 (4.1, 7.5)
Black	418	17	3,454	6.4 (3.4, 9.4)
Other	159	5	1,430	4.6 (0.6, 8.5)
Ethnicity				
Hispanic or Latino	330	12	2,851	5.5 (2.4, 8.6)
Not Hispanic or Latino	1,406	56	12,314	5.9 (4.4, 7.5)

Analyses in women ≤ 35 years

Summary of Analyses in Women ≤ 35 years



*One subject in the primary analysis population does not have BMI information.

Summary

- The effectiveness of AG200-15 in the general population does not meet the Division's previously communicated criteria (point estimate and CI upper bound exceed 5).

- The effectiveness of AG200-15 in each subgroup does not meet the criteria, even in the non-obese subjects.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Safety Profile and Benefit-Risk Considerations
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 30, 2019

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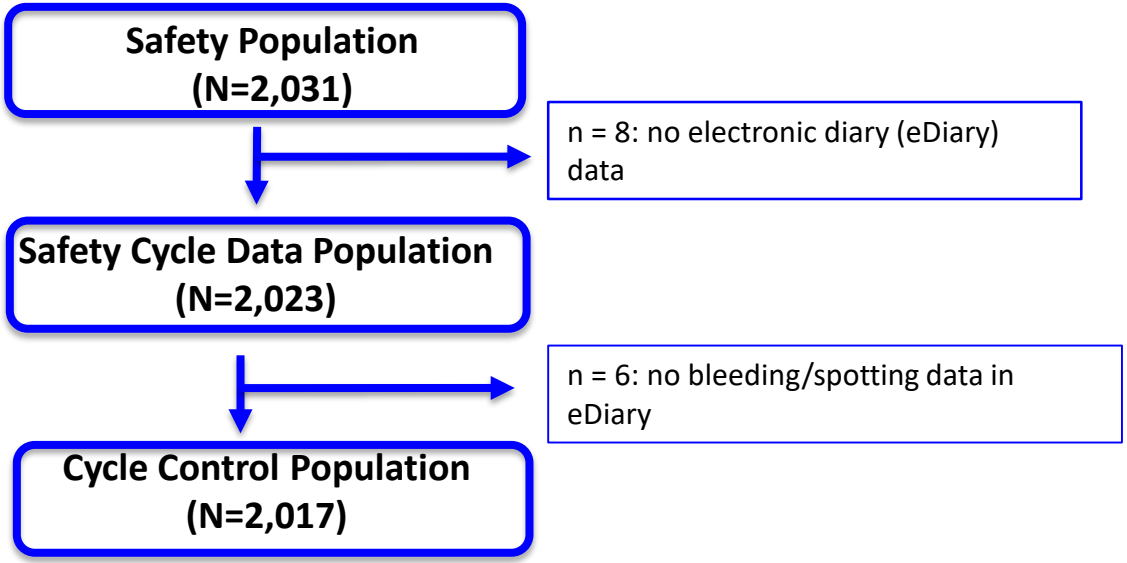
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III, Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Populations used in safety analysis for AG200-15
- VTE safety signal with AG200-15
- Applicant's Proposed Labeling
- Division's Benefit-Risk Assessment

Populations Used in Safety Analysis for AG200-15

Safety Populations in Study 23



Subject Demographics of Study 23

Characteristic		Safety Population N=2,031
BMI	Non-obese (< 30)	65%
	Obese (≥ 30)	35%
Race	White	67%
	Black	24%
	Other	9%
Ethnicity	Hispanic or Latino	19%
	Not Hispanic or Latino	81%

Subject Disposition for Study 23

Disposition	Safety Population N=2,031 n (%)
Completed the study	989 (49)
Prematurely discontinued the study	1,042 (51)
Reasons for discontinuation	
Subject's decision	310 (15)
Lost to follow-up	229 (11)
Adverse event	222 (11)
Non-compliance	116 (5.7)
Pregnancy	73 (3.6)
Other reasons	92 (4.5)

Adverse Events (AEs) of Interest for CHCs

Class labeling for CHCs includes risks for certain AEs. AEs of interest include, but not limited to:

- VTEs
- ATEs
- Liver disease
- Hypertension
- Gallbladder disease
- Depression

VTE Safety Signal with AG200-15 Use

VTE Incidence Rate with AG200-15 Use

Parameter	Applicant	Division
Studies included in analysis	Studies 12, 13, 23	Study 23
Total No. of subjects	6	5
# of subjects excluded	1	1
# of subjects with a VTE within 28 days of discontinuation	5	4
# of treatment cycles	29,900	18,841
VTE incidence rate	22 per 10,000 women-years	28 per 10,000 women-years

VTE Risk in Post-Market Setting

- Division's class labeling for CHCs states the VTE incidence rate is 3-12 per 10,000 women-years for non-oral CHC.
- Applicant concludes that the VTE incidence rate for AG200-15 is "generally in line with U.S. background rates between 15.4 to 18.9 per 10,000 women-years for a population with similar mean BMI and age." (Sponsor's clinical overview)

VTE incidence rate (clinical trial)

extrapolation

VTE risk (postmarketing observational studies)

Proposed Labeling

Proposed Labeling

- Applicant's Proposed Indication
  - AG200-15 is indicated for use by females of reproductive potential to prevent pregnancy.
- Applicant's Proposed Limitation of Use (LOU)
  - AG200-15 has demonstrated reduced effectiveness in women who weigh 202 pounds (92 kg) or more and/or have a BMI of 30 kg/m^2 or more [see Use in Specific Populations (8.9) and Clinical Studies (14)].

Proposed Limitation of Use (LOU)

LOU statement is included when there is a reasonable concern or uncertainty about a drug's benefit-risk profile.

- The Division does not believe that the Applicant's proposed LOU mitigates the Division's concerns about the overall benefit-risk profile of AG200-15 for use in the entire population.
- Further, we are uncertain that the proposed LOU would limit prescriptions to obese women

Benefit-Risk Assessment

Outline

- General benefit-risk considerations
- Dosing considerations
- Tolerability and usability considerations
- Division's assessment of benefit-risk

General Benefit-Risk Considerations

- Basis of approval for CHCs is the benefit-risk assessment
- Each investigational CHC drug for prevention of pregnancy is assessed in the context of available therapy

Benefit-Risk for AG200-15

- Concerning Pearl Index (PI) in women of higher BMI/weight
  - e.g., PI of 8.6 (5.8, 11.4) in obese women
- Concerning PI even in women of lower BMI/weight
  - e.g., PI of 4.3 (2.9, 5.8) in non-obese women
  - Higher estimated PI in overweight women
- VTE safety signal

Dosing Considerations

“Low Dose”: EE Exposure for AG200-15

Applicant

- “Low dose” product
- Exposure parameter ≈ 30 mcg EE containing oral CHC

Division

- Not a “low dose” product
- Exposure parameter ≈ 35 mcg EE containing oral CHC

LNG and VTE Risk

- The Applicant presents LNG as a “safer” progestin which may decrease VTE risk as compared to other progestins.
- LNG VTE risk not consistent across studies:
    - Epidemiologic data is heterogenous
    - Prevalent vs. new users
    - Residual confounding
    - Selective prescribing
    - Misclassification of exposure

Dosing Considerations

The Division concludes that:

- AG200-15 is not a “low dose” EE CHC product based on available therapies
- AG200-15 LNG component may not convey a safety benefit over other progestins

Tolerability and Usability Considerations

Tolerability (Cycle Control) for Study 23

Tolerability of AG200-15

- Scheduled bleeding/spotting occurs during TDS-free week
- Unscheduled bleeding/spotting occurs when TDS is applied

Unscheduled bleeding/spotting data: Division's analysis

- 60% of subjects after cycle 1
- 41% of subjects after cycle 13
- After 1 year of treatment, women still experienced unscheduled bleeding

Usability for Study 23

Usability of AG200-15

- Proposed dosing regimen is one TDS for 7-day wear for three consecutive weeks followed by one TDS free-week
- One carton contains 3 TDSs

Usability Data

- Almost 15% of all completed treatment cycles used four or more TDSs

Tolerability And Usability Summary

The Division has concerns that tolerability and usability issues could:

- outweigh the product's offered convenience
- affect compliance and sustained use

Division's Assessment Of Benefit-Risk

Division's Thinking on AG200-15

Another transdermal CHC could provide an additional alternative for women seeking a non-invasive method of contraception, but:

- AG200-15 does not meet FDA's regulatory definition of unmet need
- AG200-15 is not a "low dose" product given the availability of <20 mcg EE CHCs in the United States
- LNG component may not confer an additional "safety" benefit
- AG200-15 effectiveness is not acceptable in the general or non-obese population in the context of VTE risk and available therapy
- Product tolerability and usability issues could outweigh AG200-15's convenience
- Inclusion of an LOU in labeling does not sufficiently address the Division's overall concern regarding the benefit-risk of AG200-15

Division's Benefit-Risk Assessment of AG200-15

The Division has concerns about the benefit-risk assessment for AG200-15 in the context of available therapy.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Backup Slides Shown

Study 14 EE Exposure

Group 1: AG200-15/AG200-15/Ortho-Cyclen (OC)

Group 2: AG200-15/OC/AG200-15

	AG200-15		AG200-15		OC	
	Cycle 1		Cycle 2		Cycle 3	
Group 1 (N=17)	Week 1	Week 3	Week 1	Week 3	Week 1	Week 3
	5.2 (1.7)	6.4 (2.1)	6.2 (2.1)	7.2 (2.7)	7.5 (3.2)	7.0 (2.4)
	AG200-15		OC		AG200-15	
	Cycle 1		Cycle 2		Cycle 3	
Group 2 (N=15)	Week 1	Week 3	Week 1	Week 3	Week 1	Week 3
	4.0 (1.0)	6.0 (1.3)	6.9 (1.8)	8.0 (2.1)	3.8 (1.6)	5.2 (1.7)

	Agile Patch	Agile Patch not excluding sexually inactive cycles	Quartette
Weight <70 kg	4.3 (6.02)	4.16 (5.82)	2.59 (4.03)
Weight 70-90 kg	5.28 (7.64)	5.11 (7.40)	3.38 (5.17)
Weight > =90 kg	10.05 (13.97)	9.68 (13.47)	4.82 (7.60)