Pediatric Focused Safety Review: Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

Pediatric Advisory Committee Meeting
September 11, 2012

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Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Additional Relevant Safety Labeling
- Previous Safety Reviews
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

- **Drug:** Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)
- **Formulation:** tablets
- **Therapeutic Category:** combination oral contraceptive (COC)
- **Sponsor:** Bayer Healthcare Pharmaceuticals, Inc.

Background Drug Information
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

- **Indication**:
  - Prevent pregnancy
  - Treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception
  - Treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control
  - Raise folate levels in women who choose to use an oral contraceptive for contraception

Background Drug Information
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

- **Original Market approval:** September 24, 2010
  - Yasmin, the first drospirenone (DRSP)-containing COC, was approved on May 11, 2001. Brand products summarized below.

Trade Name	Product Presentation	Ethinyl Estradiol Dose x Days	Drospirenone Dose x Days	Levomefolate Calcium x Days
Yasmin	28 Tablets (21/28 days active)	30 mcg x 21	3 mg x 21	n/a
Yaz	24+4 Tablets (24/28 days active)	20 mcg x 24	3 mg x 24	n/a
Beyaz	24+4 Tablets	20 mcg x 24	3 mg x 24	451 mcg x 24 451 mcg x 4

Background Drug Information
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

- **Beyaz PREA labeling changes:** September 24, 2010
  - PREA studies waived in pre-menarcheal patients.
  - DRSP class labeling
    - *February 2012*: updated to include increased risk of venous thromboembolic events (VTE) upon starting and restarting COCs in Warnings and Precautions (5.1).
    - *April 2012*: updated to include **possible** increased risk of venous thromboembolic events (VTE) with COCs containing DRSP vs. levonorgestrel or other progestins in Warnings and Precautions (5.1) and Patient Information (17).

Pediatric Studies
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

- Contraception
  - The pediatric study requirement for post-menarcheal pediatric patients was fulfilled by extrapolation of efficacy from adults and leveraging existing safety and dosing information from other drospirenone products.

Pediatric Studies
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

- Acne
  - Two multicenter, double-blind, randomized, placebo-controlled studies in patients age 14-45 years of age with moderate acne received YAZ (ethinyl estradiol, drospirenone) or placebo for six 28-day cycles.
  - Patients randomized to YAZ or placebo
    - Study 1 (n=458, 62 patients age 14-17 [13.5%])
    - Study 2 (n=431, 76 patients age 14-17 [17.6%])
  - YAZ demonstrated superiority over vehicle in decline of Investigator's Static Global Assessment (ISGA) scale and lesion count from baseline.

Pediatric Labeling Changes
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

8.4 Use in Specific Populations, Pediatric Use

- Safety and efficacy of Beyaz has been established in women of reproductive age. 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.

Pediatric information included throughout labeling for post-menarcheal patients.

Relevant Safety Labeling
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

BOXED WARNING

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)

Relevant Safety Labeling
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

4 CONTRAINDICATIONS

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases
- Undiagnosed abnormal uterine bleeding
- Breast cancer or other estrogen- or progestin-sensitive cancer
- Liver tumors or liver disease
- Pregnancy

Relevant Safety Labeling
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

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

Relevant Safety Labeling
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

5 WARNINGS AND PRECAUTIONS (cont.)

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

Relevant Safety Labeling
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke *[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*)]*

Relevant Safety Labeling
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

6 ADVERSE REACTIONS

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

Relevant Safety Labeling
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- *Contraception, Acne and Folate Supplementation Clinical Trials*

  The most common adverse reactions (≥ 2% of users) were:

  headache/migraine (5.9%),
  menstrual irregularities (4.1%)
  nausea/vomiting (3.5%)
  breast pain/tenderness (3.2%).

Relevant Safety Labeling
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Serious Adverse Reactions

- Contraception Clinical Trials: migraine and cervical dysplasia
- Acne Clinical Trials: none
- Folate Supplementation Clinical Trial: cervix carcinoma stage 0

Previous Safety Reviews
Drospirenone-containing Contraceptives

- Conflicting findings from epidemiologic studies were discussed at the Joint Meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on December 8, 2011.
  - Majority of committee felt benefits of DRSP-containing COCs outweighed their risks, but the class label did not adequately reflect the risk/benefit profile.
  - Recommended information regarding the potential risk and a concise summary of the studies be included in the label.

Previous Safety Reviews Drospirenone-containing Contraceptives Summary

- Several epidemiologic studies completed 2001- 2011
  - Most included DRSP with 30 mcg Ethinyl Estradiol (EE) (Yasmin)
  - Only 1 included DRSP with 20 mcg EE (Yaz)
  - None evaluated Beyaz specifically
- VTE risk not specifically addressed among teenagers.
- Most studies included women age 15-44 years.
- All studies adjusted for age

Epidemiologic Study Populations

Design	Authors	Age Range (years)	Mean Age (years)
Cohort	Dinger 2007 (EURAS)	All ages	Yasmin 26 LNG 25 Other 25
	Seeger 2007 (Ingenix)	10-59	Yasmin 28 Comparator 28
	Lidegaard 2009, 2011	15-49	Not provided
	Sidney (FDA) 2011	10-55	Yasmin 26 LNG 28 Other 27
Case-Control	Dinger 2010 Jick 2011 Parkin 2011	15-44	Not provided Not provided Cases 32 Controls 32
	Vlieg 2009	18-50	Cases 37 Controls 37

LNG- levonorgestrel- containing COCs

Age-Specific Incidence Rates per 10,000 women-years (WY) FDA-funded Study 2001-2007

NEW USERS	Age	DROSPIRENONE			COMPARATORS*		
		WY	Events	Rate	WY	Events	Rate
VTE	10-24	39,452	19	**4.8**	103,683	32	3.1
	25-34	27,362	26	**9.5**	77,191	39	5.1
ATE**	10-24	39,452	0	0.0	103,683	5	0.5
	25-34	27,362	3	1.1	77,191	9	1.2

**COMPARATOR group includes COCs containing norethindrone, norgestimate, or levonorgestrel progestins*
***ATE- Arterial thrombotic events*

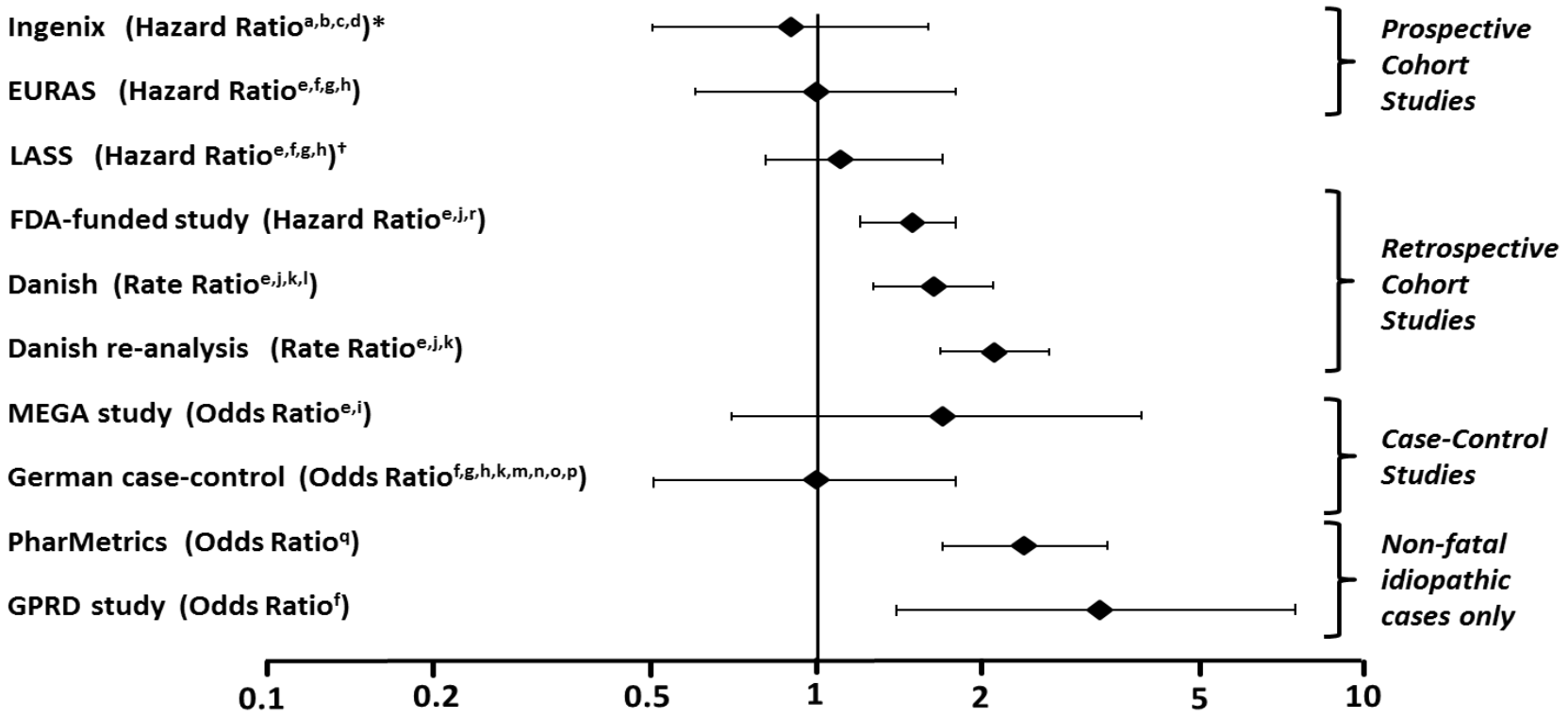
Source: Summary of tables 10a,10b, http://www.fda.gov/Drugs/DrugSafety/ucm277346.htm

VTE Relative Risk Age Interaction for Younger Yasmin Users

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

VTE Risk with Yasmin Relative to LNG-Containing COCs - Current Beyaz Label

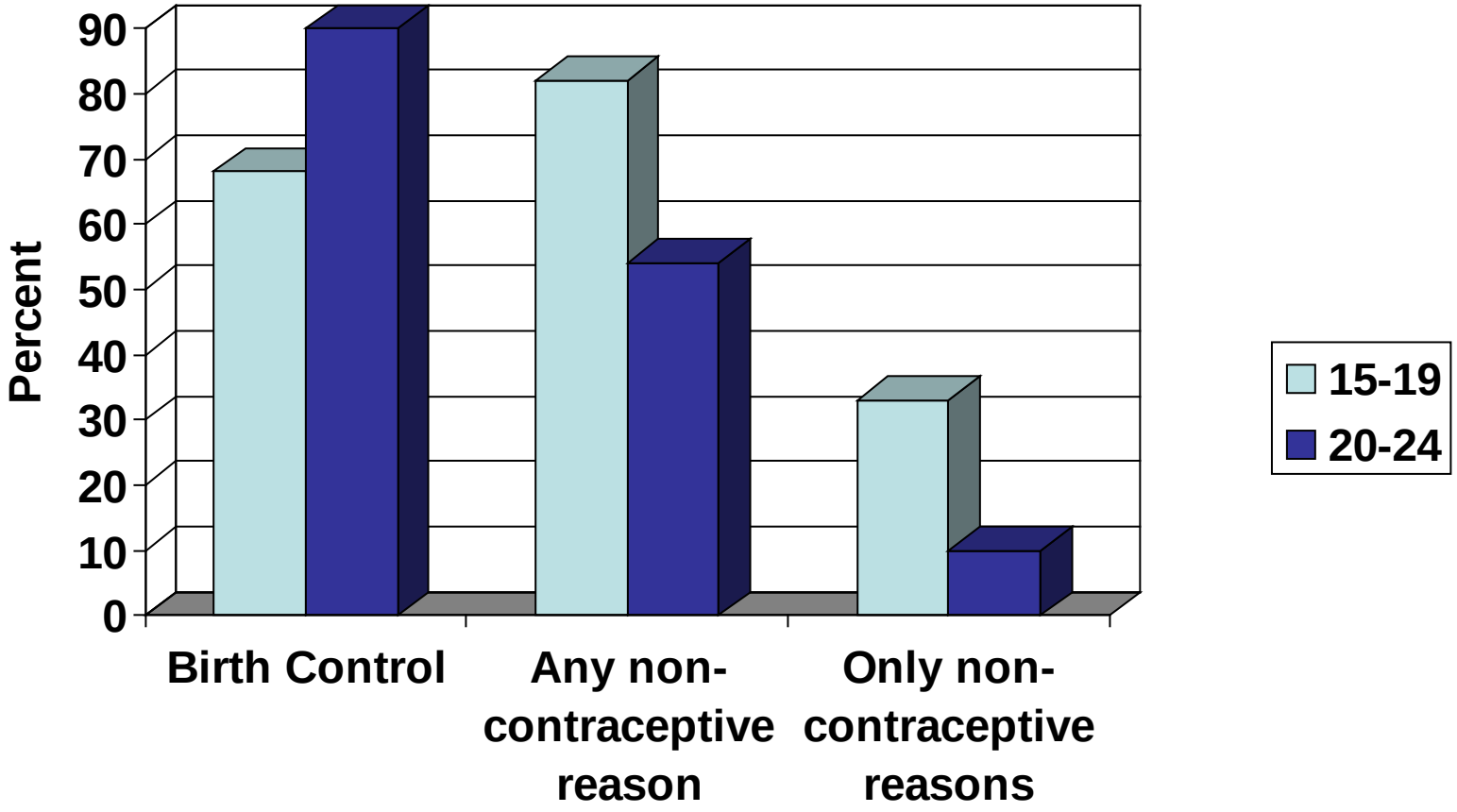


Previous Safety Reviews
Drospirenone-containing Contraceptives

Summary of Epidemiologic Studies (continued):

- Incidence rate of VTE in the one study that included the DRSP-containing COC with 20 mcg EE was similar to that for the 30 mcg EE product.
- Relative risk of VTE compared to non-users (Lidegaard et al, 2011)
  - COC with DRSP + 20 mcg EE 4.8 (95% CI:3.1-7.3)
  - COC with DRSP + 30 mcg EE 4.5 (95% CI:3.9-5.1)

Reasons for Birth Control Pill Use by Age-group



Source:Guttmacher: (Beyond Birth Control: The Overlooked Benefits of Oral Contraceptives by Rachel Jones, http://www.guttmacher.org/pubs/Beyond-Birth-Control.pdf)

Drospirenone-Containing Contraceptive Products*
Drug Utilization[1]
Outpatient Retail Pharmacies
September 1, 2010 through March 31, 2012

	Drospirenone-Containing Products			
	Prescriptions (N)	*Share (%)*	Patients (N)	*Share (%)*
Total Population	18.9 million	*100%*	2.7 million	*100%*
Pediatric Population (0-17 years)	1.6 million	*8%*	278,000	*10%*
Adults (18+ years)	17.4 million	*92%*	2.5 million	*90%*
	Beyaz®			
	Prescriptions (N)	*Share (%)*	Patients (N)	*Share (%)*
Total Population	1.6 million	*100%*	326,000	*100%*
Pediatric Population (0-17 years)	169,000	*11%*	39,000	*12%*
Adults (18+ years)	1.4 million	*89%*	293,000	*88%*

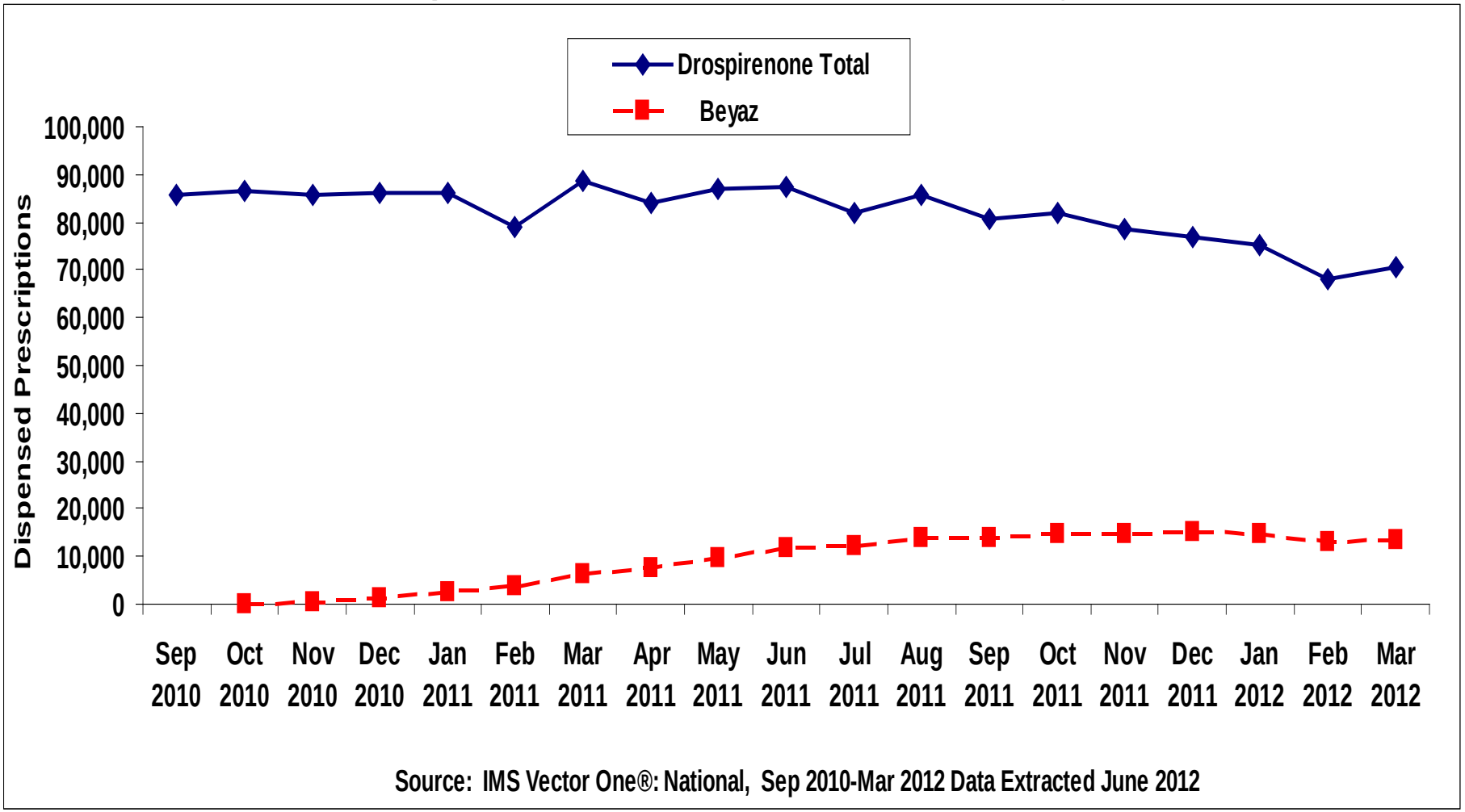
Note: IMS does not recommend adding across unique patient counts. Summing across patient age bands is not advisable and can result in overestimates of calculations.

***Products include Gianvi, Zarah, Ocella, Yaz, Beyaz, Yasmin, Loryna, Syeda, and Vestura contraceptive products**

[1]Source: IMS Vector One®: National and Total Patient Tracker, September 2010-March 2012 Data Extracted June 2012

Drospirenone-Containing Contraceptive Products

Nationally estimated number of dispensed prescriptions for all Drospirenone products and Beyaz by patient age (0-17 years) in U.S. outpatient retail pharmacies, September 1, 2010 - March 31, 2012, monthly



Source: IMS Vector One®: National, Sep 2010-Mar 2012 Data Extracted June 2012

Beyaz Drug Utilization
Outpatient Retail Pharmacies
September 1, 2010 through March 31, 2012

- Top prescribing specialty: Obstetrics and Gynecology (69% of prescriptions)[1]
  - Pediatrics <1%
- Top diagnosis codes in patients aged 14-17 years[2]:
  - Dysmenorrhea
  - Contraceptive Management-Counseling

[1]Source: IMS Vector One®: National, September 2010-March 2012 Data Extracted June 2012

[2]Source: Encuity Research, LLC., Physician Drug and Diagnosis Audit, September 2010-March 2012 Data Extracted June 2012

Total Number* of *domestic* Beyaz Adverse Event Reports Since Pediatric Approval (September 24, 2010- May 1, 2012)

	All reports	Serious**	Death
Adults (≥ 17 yrs.)	158	75	4
Pediatrics (0-16 yrs.)	19	9†	0
Unknown Age (Null values)	290	46	1†
All Ages	467	130	5

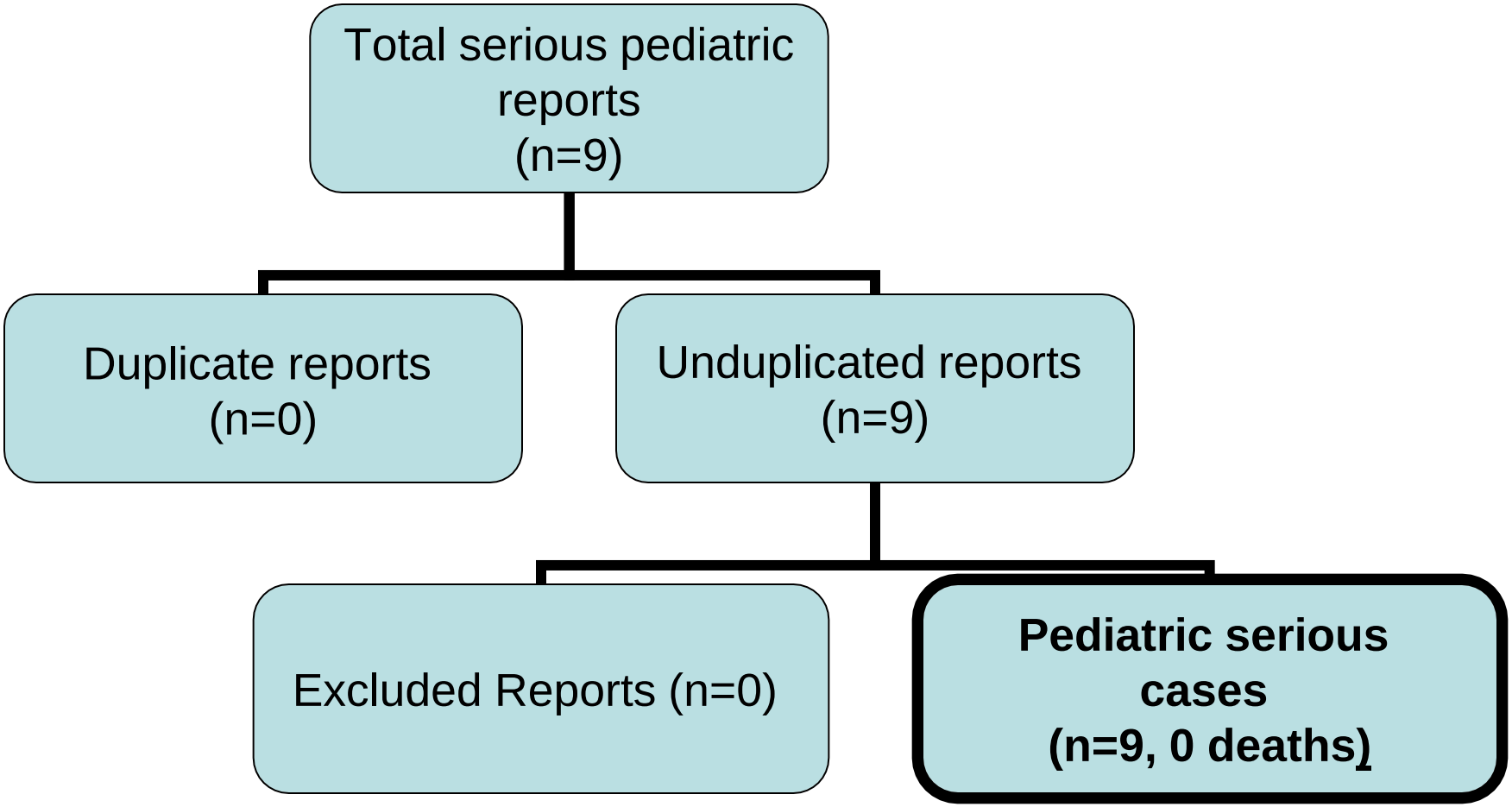
*May include duplicates and have not been assessed for causality

**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

†Insufficient clinical information to determine age

Note: Table summarized total number of *domestic* AERS reports. The AERS search did not retrieve any *foreign* reports

Case Selection



Serious Adverse Events
Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium) (n=9)

- Age (n=9)
  - 12-15 years (n=2)
  - 16-17 years (n=7)
- Deaths (n=0)
- Thromboembolic events (n=6)
- Toxic shock syndrome (TSS) (n=1)
- Syncopal episode (n=1)
- Musculoskeletal pain with anxiety (n=1)

*Unlabeled events are underlined.

Serious Non-Fatal Labeled Adverse Events Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

Thromboembolic events (n=6)

12 year-old female developed bilateral deep vein thrombosis in lower extremities and an interrupted inferior vena cava after an unspecified length of Yaz or Beyaz use.

14 year-old female experienced “face breaking out” after 2 months of Beyaz use. She was switched to Loestrin (formulation unknown) and diagnosed with VTE in the left eye 1 month later.

16 year-old female developed a VTE shortly after starting Yaz or Beyaz.

Serious Non-Fatal Labeled Adverse Events Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

Thromboembolic events (n=6) (continued)

16 year-old female hospitalized due to pulmonary embolism.

16 year-old female developed pulmonary embolism after unspecified length of Beyaz use. Previously used Ortho-Tricyclen and DepoProvera, and smoked 10 cigarettes/day.

17 year-old female developed coronary artery embolism that extended to bilateral pulmonary embolism after 2 weeks use of Beyaz. No contributing factors found.

Beyaz Labeling- Thromboembolic events noted in CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE EVENTS sections

Serious Non-Fatal Unlabeled Adverse Events Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

Toxic Shock Syndrome (TSS) (n=1)

17 year-old female with a recent history of toxic shock symptoms noted reappearance of toxic shock symptoms after an unspecified period of Beyaz use. Streptococcus test was positive.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

Syncopal episode (n=1)

15 year-old female experienced bleeding, diarrhea and abdominal bloating on Yaz and was switched to Beyaz. She experienced multiple “fainting spells” and “heart racing” after an unspecified period of Beyaz use and was seen in the ER. Results of blood work was unknown but EKG was normal. She discontinued Beyaz when she was 17 years old.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

Musculoskeletal pain and anxiety (n=1)

17 year-old female experienced intermittent pain in right shoulder and hand, especially the fingers while on Beyaz for an unspecified length of time. She reported feeling like she was having a heart attack and was anxious. No assessment was given and the reporter declined any follow-up.

Beyaz is indicated for premenstrual dysphoric disorder (PMDD) which includes symptoms such as anxiety and musculoskeletal pain.

*Unlabeled events are underlined.

Summary Pediatric Focused Safety Review Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)

- This concludes the pediatric focused safety review.
- As a result of PREA requirements, Beyaz is approved for contraception in post-menarcheal patients and for moderate acne patients 14 years and older who desire an oral contraceptive for birth control.
- The safety review identified no new signals.
- FDA recommends continuing routine monitoring.
- Does the Committee concur?

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