Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name:	Skyla (levonorgestrel-releasing intrauterine system)
Pediatric Labeling Approval Date:	January 19, 2013
Application Type/Number:	NDA 203159
Applicant/Sponsor:	Bayer Healthcare Pharmaceuticals, Inc.
OSE RCM #:	2015-1927

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Skyla in pediatric patients.

Skyla was first approved in 2013 and is indicated for prevention of pregnancy for up to 3 years. Safety and efficacy of Skyla have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal females under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.[1]

With interest in identifying rare, serious, or unlabeled events associated with Skyla use in the pediatric population, we reviewed pediatric cases with serious outcome in FAERS from April 4, 2013, to August 31, 2015.

A total of sixteen cases reported serious adverse events including bleeding pattern alteration, IUD expulsion, pregnancy and pelvic inflammatory disease. These events are consistent with the known risk in the labeling and no increased severity was observed. No pediatric deaths were identified.

In order to capture pediatric use for Skyla and to provide context for the adverse event cases submitted to the FAERS database, drug utilization patterns were assessed. Based on claims data from a sample of 131 pharmacies, 3,258 clinics, hospitals and physician offices, approximately 94% (25,330 patients) of patients with a prescription and/or procedure claim for Skyla were adults aged 18 years and older. Pediatric patients aged 0-17 years accounted for 6% (1,583 patients) of the sample population. The utilization data for Skyla was obtained from a sample of pharmacies, clinics, hospitals and physician offices and are not nationally projected. Nationwide projections are not available at this time.

We did not identify any new pediatric safety issues in this review. DPV recommends returning to routine pharmacovigilance monitoring for Skyla.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Skyla is a progestin-containing intrauterine device (IUD). Skyla was approved in 2013 for prevention of pregnancy for up to 3 years. The local mechanism by which continuously released levonorgestrel enhances contraceptive effectiveness of Skyla has not been conclusively demonstrated. However, several studies suggest multiple mechanisms that prevent pregnancy including the following: thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium.[1]

Safety and efficacy of Skyla have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal females under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.[1]

FDA determined that PREA post marketing requirement for Skyla was unnecessary for pre-menarchal patients and post-pubertal adolescent females less than 17 years of age. Bayer conducted a phase 3b trial (from September 2011 to May 2015) in adolescent women in Europe to investigate the safety of Skyla in users between menarche and the age of 18 (Protocol 14371) in accordance with the Pediatric Investigation Plan as approved by the EMA's Pediatric Committee. The study had treatment duration of 12 months with an optional follow up phase up to 3 years for all subjects completing 12 months of treatment. This study enrolled 304 women. The primary objective of this study focused on the assessment of adverse events, however, results of this study are not available yet.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

---------- CONTRAINDICATIONS ----------

- Pregnancy or suspicion of pregnancy. Cannot be used for post-coital contraception (4)
- Congenital or acquired uterine anomaly if it distorts the uterine cavity (4)
- Acute pelvic inflammatory disease (PID) or a history of PID unless there has been a subsequent intrauterine pregnancy (4)
- Postpartum endometritis or infected abortion in the past 3 months (4)
- Known or suspected uterine or cervical neoplasia (4)
- Known or suspected breast cancer or other progestin-sensitive cancer (4)
- Uterine bleeding of unknown etiology (4)
- Untreated acute cervicitis or vaginitis or other lower genital tract infections (4)
- Acute liver disease or liver tumor (benign or malignant) (4)
- Increased susceptibility to pelvic infection (4)
- A previous intrauterine device (IUD) that has not been removed (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Remove Skyla if pregnancy occurs with Skyla in place. There is increased risk of ectopic pregnancy including loss of fertility, pregnancy loss, septic abortion (including septicemia, shock and death), and premature labor and delivery. (5.1, 5.2)
- Group A streptococcal infection has been reported; strict aseptic technique is essential during insertion. (5.3)
- Before using Skyla, consider the risks of PID. (5.4)
- Bleeding patterns become altered, may remain irregular and amenorrhea may ensue. (5.5)

[1] Skyla [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; September 2013

- Perforation may occur and may reduce contraceptive effectiveness. Risk is increased if inserted in lactating women and may be increased if inserted in women with fixed retroverted uteri and postpartum. (5.6)
- Partial or complete expulsion may occur. (5.7)
- Evaluate persistent enlarged ovarian follicles. (5.8)
- Skyla can be safely scanned with MRI only under certain conditions (5.11)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions reported (>10% users) are bleeding pattern alterations, vulvovaginitis, abdominal/pelvic pain, acne/seborrhea, ovarian cyst and headache. (6)

---------- DRUG INTERACTIONS ----------

- Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the serum concentration of progestins. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Small amounts of progestins pass into breast milk resulting in detectable steroid levels in infant serum. (8.3)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. Detailed descriptions and limitations of the databases are included in Appendix A.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the settings of distribution for Skyla from August 2013 through July 2015, cumulative. Sales data for Skyla by the number of packages/cartons sold from the manufacturer to all U.S. channels of distribution indicated that approximately 91% of Skyla packages/cartons were sold to mail-order pharmacies, 8% to non-retail settings (clinics) and 1 % to retail pharmacy settings.[2] Skyla is a progestin-containing intrauterine device (IUD) inserted by a healthcare provider. Therefore, this drug utilization analysis focuses on Skyla use based on prescription and procedure claims data from a sample of pharmacies, hospitals and clinics.

2.1.2 Data Sources Used

The Symphony Health Solutions' Integrated Dataverse (IDV)™ database was used to obtain the number of unique patients with the pharmacy prescription/procedure claim for Skyla, stratified by patient age (0-8 years, 9-12 years, 13-17 and 18+ years), from August 2013 through July 2015, cumulative. National projections of this data are not available and thus the data only represent a sample of 131 pharmacies, 3,258 clinics, hospitals and physician offices.

Patient selection in Symphony Health Solutions' IDV database was based on the presence of a pharmacy prescription claim using National Drug Code for Skyla (NDC codes:50419-0422-01) and/or the presence

[2] IMS Health, IMS National Sales Perspectives™ Database. August 2013 - July 2015. Extracted September 2015. File: 2015-1927- NSP- Skyla-BPCA 09.09.2015 xlsx

of a procedure claim using the Health Care Common Procedure Coding System (HCPS code J7301) which represents administration of Skyla by a trained health care provider. Prescription and medical claims were also stratified by prescriber specialty. Selected diagnoses codes of interest were captured using the International Classification of Diseases, Ninth Revision System (ICD-9), only in patients with a diagnosis claim made within 180 days prior to or 180 days subsequent to an Skyla prescription and/or procedure claim. The selected diagnoses codes of interest were grouped into the following indications: IUD insertion/removal and contraceptive management and surveillance. (Appendix B) These diagnoses groups were selected to capture approved indications for Skyla.

2.2 RESULTS

2.2.1 Patient Demographics

Table 2.2.1 provides the total number of patients with a prescription and/or procedure claim for Skyla captured from a study sample, stratified by patient age, from August 2013 through July 2015, cumulative. During the examined time, 26,915 patients had a prescription and/or procedure claim for Skyla. Patients ages 18 years and older accounted for 94% (25,330 patients) of the total patients with a claim for Skyla. The pediatric population aged 0-17 years accounted for approximately 6% (1,583 patients) of total patients. Among pediatric patients, the largest proportion of Skyla use was in patients aged 13-17 years, accounting for approximately 99.9% (1,582 patients) of pediatric patients. Patients aged 9-12 year accounted for less than 1% (1 patient) of the total pediatric patients with a claim for Skyla. There were no patients ages 0-8 years captured in our sample.

Table 2.2.1

Total number of patients with prescription and /or procedure claims* for Skyla® from study sample, stratified by patient age***, August 2013 through July 2015, cumulative**

	Patient (N)	Share (%)
Skyla® Total	**26,915**	**100%**
0-17 years	1,583	6%
0-8 years	-	-
9-12 years	1	<0.1%
13-17 years	1,582	99.9%
18 years and older	25,330	**94.1%**
Unspecified age	2	<0.1%

* Claims are from U.S.commercial, medicare Pard D, Cash, and Medicaid plans

**Claims data from sample of-131 pharmacies & 3,258 clinics, hospitals and physician offices

*** Age is at first claim during examined time period. Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years of age (17 years and 11 months).

Source: Symphony Health Solutions' Integrated Dataverse (IDV)™ . August 2013- July 2015. Extracted November 2015. File: 2015-1927-CPA- BPCA-Skyla-2 age Parameters and Table.xls

2.2.2 Prescriber Specialty

Table 2.2.2 provides the total number of patients with a prescription and/or procedure claim for Skyla, stratified by the top prescriber specialties, from August 2013 through July 2015, cumulative. During the examined time, approximately 90% (24,132 patients) of patients with a prescription and/or procedure claim for Skyla were from Obstetrics and Gynecology. Family Medicine, General Practice and Osteopathic combined, accounted for approximately 7% (1,813 patients. Approximately 0.1% (26 patients) of the total patients with a procedure and/or prescription claim for Skyla were prescribed by pediatrics.

Table 2.2.2

Total number of patients by the top 6 prescribing specialties with a prescription and/or procedure claim* for Skyla®, from a study sample, August 2013 through July 2015, cumulative

	Patient (N)	Share (%)
Skyla Total Patients	26,891	100.0%
OB/GYN	24,132	89.7%
FM/GP/DO*	1,813	6.7%
Nurse Practitioner	281	1.0%
Emergency/Critical Care Medicine	55	0.2%
Internal Medicine	50	0.2%
Pediatrics	26	0.1%
All Others	493	1.8%

*FM: Family Medicine, GP: General Practationer, DO: Doctor of Osteopathic Medicine

**Claims are from U.S. commercial, Medicare Part D, Cash, and Medicaid plans

Source: Symphony Health Solutions' Integrated Dataverse (IDV)™. August 2013- July 2015. Extracted November 2015. File Source: SHSCPA 2015-1927 Skyla BPCA-CPA_1- Prescriber specialty- 12.02.2015 xls

2.2.3 Diagnoses Associated with Use

An analysis of the total number of patients with a prescription and/or procedure claim for Skyla and a claim for the selected diagnosis codes of interest from August 2013 through July 2015 was also conducted. A total of 26,325 patients (98% of sample population) were captured with both a prescription/ procedure claim for Skyla and a claim for a selected diagnosis during the defined time period. Among 26,325 total patients captured with one or more of the diagnoses codes of interest, the adult population aged 18 years and older accounted for the majority of patients with approximately 94% (24,784 patients) of total patients. Pediatric population aged 0-17 years accounted for approximately 6% (1,539 patients) of total patients. All the pediatric patients (1,539 patients) captured in this sample had a diagnosis code for either insertion/removal of intrauterine device and/or contraceptive management/surveillance of intrauterine device (data not shown)[3].

[3] Symphony Health Solutions' Integrated Dataverse (IDV) ™. August 2013- July 2015. Extracted December 2015. File: SHSCPA 2015-1927 Skyla, 12-01.2015

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix C for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of Search	September 14, 2015
Time Period of Search	April 4, 2013[*] - August 31, 2015
Search Type	Profile report
Product Name(s)	Product Name(s): Skyla
Additional Criteria	Product Verbatim: Jaydess
Search Parameters	All ages, all outcomes, worldwide

[*] *FDA receive date for the first Skyla report in FAERS*

3.2 RESULTS

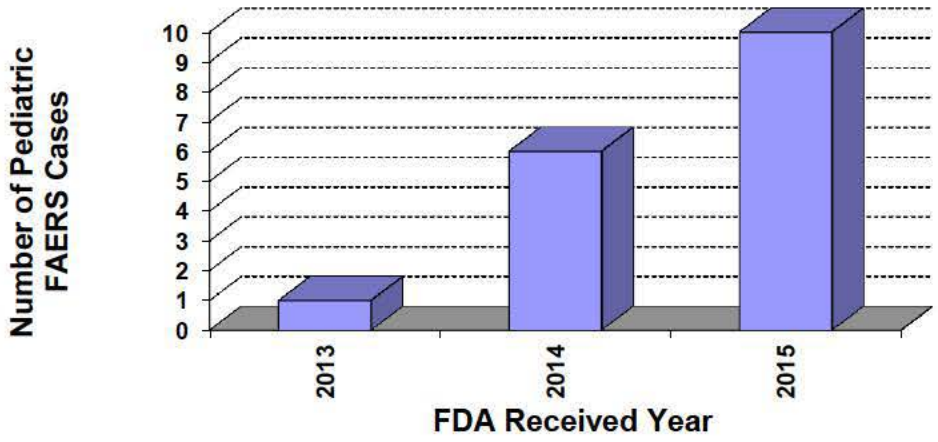
3.2.1 Total number of FAERS cases by Age

Table 3.2.1 Total Adult and Pediatric FAERS cases* April 4, 2013[§] - August 31, 2015 with Skyla

	All reports (US)	**Serious[†] (US)**	**Death (US)**
Adults (≥ 18 years)	577 (559)	223 (206)	0 (0)
Pediatrics (0 - <18 years)	46 (44)	17[‡] (15)	0 (0)

** May include duplicates and transplacental exposures, and have not been assessed for causality*
[§] *FDA receive date for the first Skyla report in FAERS*
[†] *Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.*
[‡] *See Figure 3.2.2*

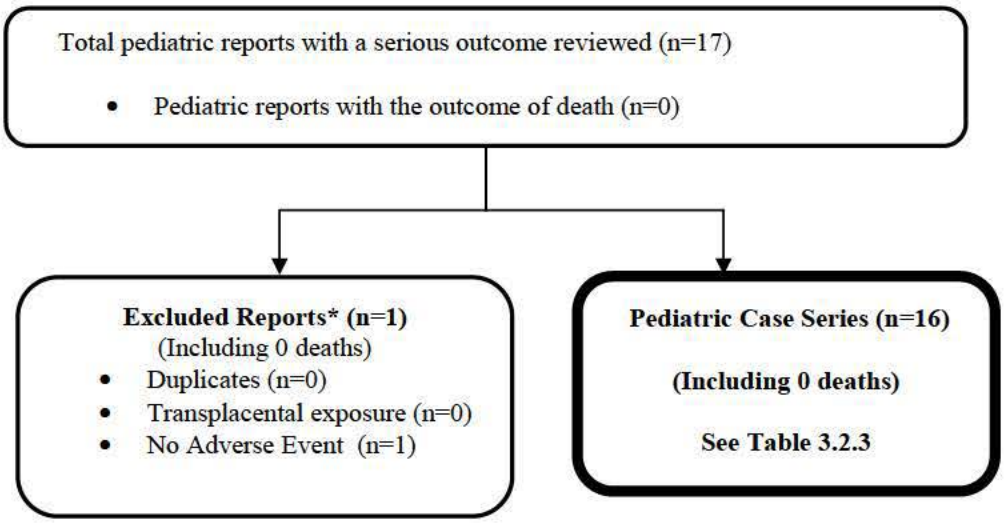
Figure 3.2.1 Serious Pediatric Reports for Skyla, by year of FDA receipt [April 4, 2013 - August 31, 2015] (n=17)



3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 17 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Skyla



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.

3.2.3 Characteristics of Pediatric Case Series

Appendix D lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Skyla (N=16)

Age (n=16)	0 - < 1 month	0
	1 month - <2 years	0
	2- < 6 years	0

Table 3.2.3 Characteristics of Pediatric Case Series with Skyla (N=16)		
	6- <12 years	0
	12- < 18 years	16
Sex	Male	0
	Female	16
	Unknown	0
Country	United States	14
	Foreign	2
Reported Indication*	Contraception	13
	Menometrorrhagia	1
	Menstrual disorder	1
	Unknown	1
Serious Outcome†	Death	0
	Life-threatening	0
	Hospitalized	1
	Disability	0
	Congenital anomaly	0
	Other serious	15

***** Reported indication- the information that was provided in the indication field of the Medwatch report.

† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

No pediatric deaths were identified.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=16)

A total of sixteen cases reported serious adverse events including bleeding pattern alteration, IUD expulsion, pregnancy, and pelvic inflammatory disease. These events are consistent with the known risk in the labeling and no increased severity was observed. The reported age of users ranged from 15 to 17 years (mean [standard deviation (SD)] 16 years [0.78 year]). All patients were of female sex. Two cases include more than one event (1 case reported both IUD expulsion and pregnancy, and the other case reported both heavy bleeding and IUD expulsion).

3.4.1 Labeled Event: Bleeding pattern alterations (n =4)

"Bleeding pattern alterations" are labeled under the Warnings and Precautions section. A total of four cases noted bleeding pattern alterations and resulted in irregular spotting, frequent bleeding, or heavy bleeding after Skyla insertion. Within these four cases, one included a 16-year-old female who experienced heavy bleeding after Skyla insertion and complete expulsion of Skyla after one month. The patient received a new Skyla unit and the heavy bleeding resolved. However, she then experienced irregular spotting for unknown duration. Frequent bleeding was reported in two cases with 17-year-old females during the first three months after Skyla insertion. The label notes that the number of bleeding and spotting days may be higher during the first 3-6 months of Skyla use. The remaining report of a 15-year-old lacked clinical details to assess the bleeding pattern changes.

3.4.2 Labeled Event: IUD expulsion (n=11)

"IUD expulsion" is labeled in the Warnings and Precautions section. A total of eleven cases noted IUD expulsion (eight partial and three complete expulsions) and most of these cases were US cases [US (10) and foreign (1)]. Within these eleven cases, ten cases provided details to determine the time-to-onset of expulsion from insertion.

This includes one report with an IUD expulsion immediately after insertion in a 17- year- old female. Subsequently, the patient received a new Skyla unit on that same day. Furthermore, Bayer conducted an assessment with the reported lot number due to concern of usability issue and concluded that there is no relationship between the reported event and a quality defect. Among the remaining nine cases with reported time-to-onset of expulsion, one report noted two IUD expulsions one at 54 days (initial Skyla unit) and again at 14 days after a new Skyla unit was inserted due to previous IUD expulsion. In these nine cases, IUD expulsion occurred between 14 and 197 days (median 49 days) after Skyla insertion in age of users ranged from 15 to 17 years (mean 16 years). These events are consistent with the known risk in the labeling and no increased severity was observed in these cases.

Finally, the case that did not provide details on time-to-onset of expulsion noted unintended pregnancy in a 17-year-old female who received Skyla. The patient presented with nausea and bleeding 15 months after insertion and was noted to have a positive pregnancy test. However, Skyla was not detected on ultrasound and it was determined Skyla was completely expelled at an unknown time after insertion.

3.4.3 Labeled Event: Pregnancy (n=2)

"Intrauterine pregnancy" is labeled in the Warnings and Precautions section. A total of two cases reported unintended pregnancy and one of these cases was associated with complete expulsion of IUD as previously described above in section 3.4.2. In the other case, pregnancy was confirmed 10 months after Skyla insertion and Skyla was removed when pregnancy was confirmed. No further information, such as weight or outcome of pregnancy, was provided.

3.4.4 Labeled Event: Pelvic Inflammatory Disease (n=1)

Pelvic inflammatory disease (PID) is labeled in the Warnings and Precautions section for Skyla. IUDs have been associated with an increased risk of PID, particularly during the first three weeks after insertion, most likely due to organisms being introduced into the uterus during insertion. [1, 4] Risk factors for PID include previous history of STDs or prior PID, and factors associated with STD acquisition, such as younger age, having multiple sex partners, and inconsistent use of condoms during sex. [4]

One case reported PID after Skyla insertion due to Chlamydia in a 17-year-old female who started Skyla on an unknown date and developed PID on an unspecified date. The patient was hospitalized for 48 hours, however, no further information regarding hospitalization was provided. While a number of different organisms may cause or contribute to PID, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* have been involved in a third to a half of PID cases. [4] This case lacks details to assess other risk factors for PID such as time-to-onset of PID from Skyla insertion, number of sex partners, and prior history of PID and STD limiting the ability to draw a drug-event association with Skyla and PID.

[4] Center for Disease Control and Prevention. Pelvic Inflammatory Disease (PID) - CDC Fact Sheet. Available at: http://www.cdc.gov/std/pid/stdfact-pid-detailed htm. Last updated May 4, 2015. Accessed December 3, 2015.

4 DISCUSSION

Drug utilization patterns for Skyla were examined in order to assess pediatric use and to provide context for the 16 adverse event cases submitted to the FAERS database. Our drug utilization analysis showed that the pediatric population accounted for approximately 6% (1,583 patients) of total patients with a prescription and/or procedure claim for Skyla in our sample that spanned the time period from August 2013 through July 2015. Among pediatric patients, nearly all patients were ages 13-17 years (1,582 patients). Obstetrics and Gynecology were the top prescribing specialties for Skyla. Of note, the utilization data provided in this review was obtained from a sample of 131 pharmacies, 3,258 clinics, hospitals and physician offices and are not nationally projected. Therefore, it is unknown whether these data are representative of Skyla use in the entire U.S.

With interest in identifying rare, serious, or unlabeled events associated with Skyla use in the pediatric population, we reviewed pediatric cases with serious outcome in FAERS from April 4, 2013, to August 31, 2015.

Of the sixteen cases reviewed in pediatric patients, there were no new safety signals identified, and no increased severity or frequency of any labeled adverse events.

5 CONCLUSION

We identified sixteen serious pediatric cases in the FAERS database; no deaths were reported. Based on this pediatric review, there is no evidence from these data that there are new pediatric safety concerns with Skyla.

6 RECOMMENDATIONS

DPV recommends returning to routine pharmacovigilance monitoring for Skyla.

7 REFERENCES

1. Skyla [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; September 2013

2. IMS Health, IMS National Sales Perspectives™ Database. August 2013 - July 2015. Extracted September 2015. File: 2015-1927- NSP- Skyla-BPCA 09.09.2015.xlsx

3. Symphony Health Solutions' Integrated Dataverse (IDV) ™. August 2013- July 2015. Extracted December 2015. File: SHSCPA 2015-1927 Skyla, 12-01.2015

4. Center for Disease Control and Prevention. Pelvic Inflammatory Disease (PID) - CDC Fact Sheet. Available at: http://www.cdc.gov/std/pid/stdfact-pid-detailed.htm. Last updated May 4, 2015. Accessed December 3, 2015.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market, include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from the drug utilization analysis should be interpreted in the context of the known limitations of the databases used. Based on sales data, the majority of Skyla was distributed to non-retail settings (primarily clinics). These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

Symphony Health Solutions' Integrated Dataverse (IDV)™

The Symphony Health Solutions' Integrated Dataverse (IDV) contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 220 million unique prescription patients of with an average of 4.2 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 140 million prescription drug patients are linked to a diagnosis. The overall sample represents over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

Data from Symphony Health Solutions' IDV provides patient counts with a procedure and/or pharmacy prescription claim for Skyla from a sample of approximately131 pharmacies, 3,258 clinics, hospitals and physician offices specialty pharmacies clinics, hospitals and physician offices. The universe of mail-order and specialty pharmacies contributing to these data are unknown; therefore, nationwide projections are not available at this time, and it is unknown whether these data are representative of Skyla use in the entire U.S.

Selected diagnoses of interest were captured using ICD-9 codes in the healthcare claims database for approximately 98% of the patients in the total sample of patients with a Skyla procedure and/or prescription claim. However, the identification of diagnoses using claims data is limited as it is not a directly linkage between drug and diagnosis and diagnosis data for all patients in the sample is rarely captured. Furthermore, it is likely that patients may have a claim for more than one of the selected diagnoses. Therefore, summing patients across different diagnoses is not advisable and may result in overestimates of patient counts. In addition, the data used in our analysis was not validated in medical records. As such, the estimates may be an overestimate of the true number of patients as provisional diagnoses may have been included.

8.2 APPENDIX B. DRUG UTILIZATION STUDY PARAMETERS

Diagnosis Group	ICD-9 Diagnosis Codes
IUD Insertion/removal	V25.13 REMOVE/INSERT IUD V25.12 REMOVAL OF IUD V45.51 PRSC NTRUTR CNTRCPTV DVC V25 1 INSERTION OF IUD V25.11 INSERTION OF IUD V25.02 INITIATE CONTRACEPT NEC
Contraceptive Management	V25.04 COUNSEL NATURAL FAMILY PLAN V25.4 CONTRACEPTIVE SURVEILLANCE V25 9 CONTRACEPTIVE MANGMT NOS V25.8 CONTRACEPTIVE MANGMT NEC V25.09 CONTRACEPTIVE MANGMT NEC V25 CONTRACEPTIVE MANAGEMENT V25.0 CONTRACEPTIVE COUNSELING V25.40 CONTRACEPT SURVEILL NOS V25.49 CONTRACEPT SURVEILL NEC V25.03 CONTRACEPT MGMT-EMERGNCY V45.59 PRSC OTHER CNTRCPTV DVC V45 5 PRESENCE CONTRACEPTIVE DEV V25.42 IUD SURVEILLANCE

8.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH SKYLA (N=16)

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
11130615	1	US-BAYER-2015-260731
11147813	1	US-BAYER-2015-279082
11239088	2	US-BAYER-2015-370566
11331287	1	RO-BAYER-2015-377885
11369058	1	US-BAYER-2015-394480
9995373	1	US-BAYER-2014-036421
10192425	1	US-BAYER-2014-071930
10192441	1	US-BAYER-2014-077171
10379362	1	US-BAYER-2014-119305
10600856	1	US-BAYER-2014-173357
10635625	1	US-BAYER-2014-179731
10877358	3	US-BAYER-2015-030726
10945385	4	US-BAYER-2015-060518
11106186	1	ES-BAYER-2015-214829

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
11375515	2	US-BAYER-2015-394101
9400663	1	US-BAYER-2013-085305

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH E KANG
02/18/2016

NABILA SADIQ
02/18/2016
Drug Use data was cleared on 02/16/2016

MOHAMED A MOHAMOUD
02/18/2016

NEHA GADA
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GRACE CHAI
02/19/2016

STEVEN C JONES
02/19/2016