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Office of Surveillance and Epidemiology**

Pediatric Postmarketing Adverse Event Review

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Subject: Pediatric Postmarketing Adverse Event Review

Drug Name(s): Plan B (levonorgestrel, 0.75 mg tablet)
Plan B One-Step (levonorgestrel, 1.5 mg tablet)

Pediatric Exclusivity
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EXECUTIVE SUMMARY

In accordance with Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance II (DPV II) was asked to summarize post-marketing reports of adverse events associated with the use of Plan B (levonorgestrel) in pediatric patients (17 years of age or younger). This review focuses on reports in pediatric patients with fatal outcomes or serious unlabeled adverse events with Plan B (levonorgestrel, 0.75 mg) or Plan B One-Step (levonorgestrel 1.5 mg).

Plan B is an oral progestin indicated for emergency contraception available as a single 1.5 mg tablet (Plan B One-Step) or two 0.75 mg tablets, taken 12 hours apart. Plan B and Plan B One-Step are available only by prescription for women younger than age 17 years, and available over the counter for women 17 years and older. The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) from January 1, 2002 up to the "data lock" date of December 31, 2010. AERS contained 252 reports for any Plan B (levonorgestrel) formulation. Pediatric reports represent approximately 7.5% of the total (19/252).

This postmarket evaluation found no evidence of pediatric safety concerns with Plan B (levonorgestrel). DPV II will continue pharmacovigilance activities associated with Plan B (levonorgestrel).

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

In this review, any mention of Plan B refers to either Plan B or Plan B One-Step products.

Plan B (levonorgestrel) is a progestin-only emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Plan B was originally approved in 1999 as a two dose regimen, 0.75 mg to be taken 12 hours apart. On July 10, 2009, FDA approved Plan B One-Step as a new single dose 1.5 mg tablet. Plan B and Plan B One-Step are available only by prescription for women younger than age 17 years, and available over the counter for women 17 years and older. All Plan B products are not intended for routine use as a contraceptive.

1.2 PEDIATRIC FILING HISTORY

A pediatric labeling change occurred following the FDA approval of Plan B One-Step, a new single dose tablet and new dosage regimen.

1.3 PEDIATRIC LABELING

Current labeling for Plan B One-Step includes:

Safety and efficacy of progestin-only pills for long-term contraception have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents less than 17 years and for users 17 years and older. Use of Plan B One-Step emergency contraception before menarche is not indicated.

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) database was searched with the strategy described in Table 1 (see Appendix A).

Table 1: AERS Search Strategy*	
Date	August 29, 2011
Time period	January 1, 2002 -- December 31, 2010
Drug Names	Plan B and Plan B One-Step (levonorgestrel)
Additional criteria	Refer to Appendix A

* See Appendix B for description of the AERS database.

3 RESULTS

3.1 COUNTS OF AERS REPORTS

Table 2: Counts¹ of AERS Reports for any Plan B formulation (levonorgestrel)			
From January 1, 2002 -- December 31, 2010			
	All reports (US) ²	Serious ³ (US)	Death (all US reports)
Adults (≥ 18 yrs.)	200 (190)	182 (174)	4
Pediatrics (0-17 yrs.)	19 (19)	18 (18) ⁴	1
Age unknown (Null values)	33 (24)	30 (23)	0
Total	252 (233)	230 (215)	5

¹ May include duplicates

² US counts in parentheses

³ 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.

⁴ See Figure 2

3.2 SELECTION OF PEDIATRIC AERS CASES

The above AERS search strategy retrieved 18 pediatric reports reporting a serious outcome, not all of which involved Plan B ingestion by a pediatric patient. A total of 5 reports were not included in the final case series for the following reasons:

- 5 *unassessable* reports of transplacental exposure after patients took Plan B
 - one fatality in a premature infant which is acknowledged in a previous DPV postmarket review¹ (ISR #5592810)
 - two additional premature births (ISR #6396318 and ISR #6548950)
 - two reports of a miscarriage (ISR #5766016 and ISR #6607396)

The remaining pediatric patients (N=13) exposed to any Plan B formulation who reported serious outcomes are discussed in **Section 3.2**. There were no deaths among these 13 pediatric cases.

3.3 CASE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 3 summarizes the 13 AERS cases from the Pediatric Case Series with **Plan B (levonorgestrel)**.

Appendix C contains AERS Case numbers / ISR numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3: Case characteristics of pediatric case series. From January 1, 2002 -- December 31, 2010 (N=13)	
Age (n=13)	15 years (2), 16 years (7), 17 years (4)
Gender	All Female
Country of occurrence	All United States
Report Year	2003 (1), 2007 (2), 2008 (7), 2009 (3)
Dose ¹	Two doses (11) Single dose (2)
Indications	Emergency Contraception (13)
Most Commonly Reported Preferred Terms (PT)	Haematemesis (4), Vomiting (3), Menstruation Irregular (3), Loss of Consciousness (3), Abdominal Pain (3), Drug Ineffective (3), Syncope (2), Dizziness (2)
Event date	2003 (1), 2004 (1), 2007 (3), 2008 (5), 2009 (3)
Outcome ²	Hospitalized (3) Other serious (10)

¹Plan B=0.75 mg tablets taken 12 hours apart; Plan B One Step=single dose 1.5 mg tablet taken once

²Serious 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. A report may have one or more (>1) outcome.

4 DISCUSSION OF PEDIATRIC CASE SERIES

A postmarket assessment of pediatric cases (N=13) finds no significant changes in the severity of adverse events that indicate a clinically significant change in the known safety profile of Plan B (levonorgestrel). This pediatric postmarket review shows hematemesis, loss of consciousness, and syncope as potential safety signals (unlabeled adverse events). However, as previously identified in postmarket reviews with Plan B^{1,2,3}, the reviewer finds a causal relationship between these events and levonorgestrel as unassessable since the reports lack clinically meaningful information necessary for evaluation. These potential safety signals are discussed further below.

4.1 SUMMARY OF SELECTED PEDIATRIC ADVERSE EVENTS

4.1.1 HEMATEMESIS (N=4)

The AERS cases coded as “haematemesis” were patients who took Plan B and experienced either nausea or dizziness and vomiting of blood. Consistent with two previous postmarket reviews^{1,2}, this pediatric review finds a causal relationship between hematemesis and Plan B difficult to assess based on the subjective nature and lack of sufficient medical information in the AERS reports. Hematemesis can result from a number of clinical situations including forceful or recurrent vomiting, or ulcers in the gastrointestinal tract, and there is not sufficient clinical data from the AERS reports to suggest that Plan B is the direct cause of the hematemesis.

4.1.2 LOSS OF CONSCIOUSNESS (N=3) AND SYNCOPE (N=2)

A previous postmarket review³ noted “syncope” or “loss of consciousness” as potential safety signals or events of concern. The reviewer believes the above adverse events were not due to levonorgestrel exposure, but most likely caused by a strong vagal stimulation from severe abdominal pain (labeled AE) or severe dizziness (labeled AE) which led to fainting, or orthostatic hypotension. Notwithstanding above, more clinical information is necessary in order to provide a more robust evaluation of these adverse events.

5 CONCLUSION

This postmarket evaluation found no evidence of pediatric safety concerns with Plan B (levonorgestrel).

6 RECOMMENDATIONS

DPV II will continue pharmacovigilance activities associated with Plan B (levonorgestrel).

7 REFERENCES

1. Miller M, Truffa M, Boucher B, Dal Pan G. Update on Serious Adverse Events since 03/2008. Plan B (levonorgestrel), NDA 21-045. June 19, 2009; RCM#2009-949.
2. Rubio T, Davis D, Gassman A, Boucher B. New Drug Application Postmarket Evaluation Background Document for Non-New Molecular Entities (non-NME). Plan B One-Step, NDA 21-998. June 13, 2011; RCM#2009-1994.
3. Rothstein AM, Truffa M. Postmarketing safety review of Plan B, NDA 21-045. April 7, 2008. RCM#2008-470

8 APPENDICES

8.1 APPENDIX A: STANDARD SEARCHES

- A. Adults (18 yrs and above)
 - 1. All outcomes from approval date (no set criteria)
 - 2. Serious outcomes from approval date
 - 3. Death as an outcome from approval date

- B. Ages 0-17 yrs ONLY
 - 1. Same as above 1-3

8.2 APPENDIX B: ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE DESCRIPTION

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do 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 all adverse event reports that occur 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, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

8.3 APPENDIX C: AERS CASE NUMBERS/ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR PEDIATRIC CASE SERIES

	ISR number	Case number	Manufacturer Control number	FDA received date	Report Type	Age	Reported Outcome	Event date	Reported Preferred Terms (PT) or adverse event terms
1	5298411	6295990	12130	9-Apr-07	Expedited (15-Day)	16	OT	23-Mar-07	FALL,LOSS OF CONSCIOUSNESS
2	5574273	6521034	21478	21-Dec-07	Expedited (15-Day)	17	OT	7-Dec-07	CHEST DISCOMFORT,VOMITING,CHEST PAIN,DYSPNOEA
3	5805767	6703089	29847	8-Jul-08	Expedited (15-Day)	15	OT	25-Jun-08	HAEMATEMESIS,DECREASED APPETITE,DIZZINESS,ABDOMINAL PAIN UPPER
4	6408595	7303442	US-TEVA-212795USA	21-Oct-09	Expedited (15-Day)	16	OT	19-Oct-09	DRUG INEFFECTIVE,PREGNANCY AFTER POST COITAL CONTRACEPTION,HAEMATEMESIS
5	4092972	5733802	CTU 190911	15-Apr-03	Direct	16	OT	10-Apr-03	DRUG INEFFECTIVE,UNINTENDED PREGNANCY
6	5897563	6782253	18839	29-Aug-08	Periodic	16	HO	1-Jan-04	ABDOMINAL PAIN,VOMITING
7	5727449	6643262	26655	30-Apr-08	Expedited (15-Day)	16	OT	15-Apr-08	SYNCOPE,BLOOD PRESSURE DECREASED,LOSS OF CONSCIOUSNESS,ABDOMINAL PAIN,LACERATION,
8	5834184	6727731	31363	1-Aug-08	Expedited (15-Day)	16	OT	27-Jul-08	DIZZINESS,SYNCOPE
9	5912983	6789795	34270	6-Oct-08	Expedited (15-Day)	17	OT	23-Sep-08	LOSS OF CONSCIOUSNESS,EPISTAXIS, PELVIC PAIN
10	6231375	7303434	US-TEVA-197535USA	16-Jun-09	Expedited (15-Day)	17	OT	7-Jun-09	MENSTRUATION IRREGULAR,HAEMATEMESIS
11	5897564	6782254	18916	29-Aug-08	Periodic	15	HO	12-Sep-07	MENSTRUATION IRREGULAR,ABDOMINAL PAIN
12	5934830	6806560	35511	27-Oct-08	Expedited (15-Day)	17	HO	16-Oct-08	DYSPEPSIA,OVERDOSE
13	6330193	7097926	US-TEVA-206917USA	27-Aug-09	Expedited (15-Day)	16	OT	19-Aug-09	HAEMATEMESIS,VOMITING,MENSTRUATION IRREGULAR,NAUSEA,MENSTRUAL DISORDER

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