

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-998

OTHER REVIEW(S)



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

Date: June 24, 2009

To: Andrea Leonard-Segal, MD, Director
Division of Nonprescription Clinical Evaluation

Scott Monroe, MD, Director
Division of Reproductive and Urologic Products

Through: Carlos M Mena-Grillasca, RPh, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: LaToya Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Plan B One-Step (Levonorgestrel) Tablet, 1.5 mg

Application Type/Number: NDA 21-998

Applicant/sponsor: Duramed

OSE RCM #: 2009-778

1 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the Plan B One-Step labels and labeling submitted on June 9, 2009 (see Appendix A). For comparison, DMEPA referenced the labels and labeling for the currently marketed Plan B product.

2 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be improved to minimize the potential for medication errors. We provide recommendations on the label and labeling in Section 2.1 *Comments to the Division*. Section 2.2 *Comments to the Applicant* contains our recommendations for the labels and labeling. We request the recommendations in Section 2.2 be communicated to the Applicant prior to approval.

2.1 COMMENTS TO THE DIVISION

A. Carton Labeling: (Retail and Clinic Use)

DMEPA notes inconsistencies in the presentation of information on the packaging of the proposed product, Plan B One-Step and the currently marketed Plan B.

On the Principal Display Panel, the statement, "Plan B Should Be Used In Emergencies" is present on the labeling for Plan B, however this information is not present on the proposed labeling for Plan B One-Step.

DMEPA defers to the Clinical team for a decision regarding the inclusion of this information.

2.2 COMMENTS TO THE APPLICANT

A. Insert Labeling

FULL PRESCRIBING INFORMATION

Section 3 DOSAGE FORMS AND STRENGTHS

Revise the statement to include the strength of the tablet. Revise to read, "The Plan B One-Step tablet is supplied as an almost white, round tablet containing 1.5 mg of levonorgestrel and is marked G00 on one side."

B. Container Label and Carton Labeling: (Retail and Clinic Use)

There is no space indicated for the placement of the Expiration date and Control number for the product. Modify the label and labeling to include this information.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

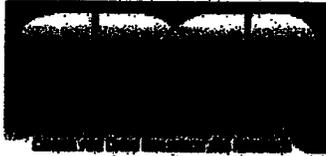
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/s/

LaToya S Toombs
6/24/2009 04:18:57 PM
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DRUG SAFETY OFFICE REVIEWER



OTC Drug Labeling Review Addendum

Office of Nonprescription Products (ONP)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-998

Submission Date: July 8, 2009

Type of Submission: N-000-B2

Sponsor: Duramed Research Inc.

Drug Product: Plan B One-Step Emergency Contraceptive

Active Ingredient: •Levonorgestrel tablet, 1.5 mg in each tablet

Indications: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 1 tablet (one dose), 1.5 mg levonorgestrel in each tablet

Review Date: July 9, 2009

Reviewer: Arlene Solbeck
IDS, DNRD

Project Manager: Leah Christl
ADRA, ONP

Timeline for OTC Labeling Negotiations

Reference is made to the following label reviews for Plan B One-Step (NDA 21-998):

- Label review for NDA 21-998 which was placed in DFS on June 17, 2009 (based on label review submitted on 6/9/09).
- Label review (Addendum) for NDA 21-998 which was placed in DFS on June 19, 2009.
- Revised labeling submitted by sponsor on 6/22/09.

- Labeling comments sent to the sponsor via memo dated July 2, 2009 asking for labeling revisions regarding the age presentation on the cartons and consumer information leaflet, and to incorporate additional comments provided by the Division of Drug Marketing, Advertising, and Communications.
- Revised labeling submitted by sponsor via email on 7/2/2009.
- Labeling comments sent to sponsor by email on 7/6/09 in response to receipt of their revised labeling sent on 7/2/2009.
- Revised labeling received from sponsor on 7/7/09 via email in response to our email of 7/6/09 requesting revisions to labeling.
- Labeling comments sent to sponsor by email on 7/8/09 in response to their revised labeling sent on 7/7/09.
- Receipt of current submission of July 8, 2009 with response to our 7/8/09 request for revised labeling.

Reviewer's Comments and Recommendations

On July 8, 2009, the sponsor sent FDA final revised labeling for the retail carton, clinic carton, and consumer information leaflet for NDA 21-998 (Plan B One-Step), the one dose regimen of levonorgestrel tablets (1.5 mg in each tablet).

We find the three labeling components in this submission to be acceptable for approval of this supplement.

Also, remind the sponsor to delete the statement "NEW! Now only ONE dose" 6 months after introduction into marketplace.

Arlene Solbeck
IDS
DNRD

Marina Chang
IDS Team Leader
DNRD

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Arlene Solbeck
7/9/2009 08:50:36 AM
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7/9/2009 08:56:23 AM
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 19, 2009

To: Scott Monroe, MD, Director
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Through: Melissa M. Truffa, RPh, Team Leader
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Robert M. Boucher, MD, MPH, FACS
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Division of Pharmacovigilance II
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Gerald Dal Pan, MD, MHS
Director, Office of Surveillance and Epidemiology (OSE), CDER

From: Mark Miller, PharmD, Safety Evaluator
Division of Pharmacovigilance II (DPV II)

Subject: Update on Serious Adverse Events since 03/2008

Drug Name(s): Plan B (levonorgestrel)

Application Type/Number: NDA 21-045

Applicant/sponsor: Duramed Pharmaceuticals

OSE RCM #: 2009-949

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EXECUTIVE SUMMARY

In response to a request from the Office of Executive Secretariat on May 11, 2009, the Adverse Event Reporting System (AERS) database was searched for Plan B adverse event reports.

This safety review is an update of a comprehensive review of Plan B completed by the Division of Pharmacovigilance (DPV) in April 2008. The reviewer evaluated new safety signals associated with Plan B since April 2008 focusing on fatalities, new AERS and data mining results, and serious unlabeled adverse events. The review also includes a summary of all adverse event reports in patients less than 18 years of age received since 1999 market approval.

An AERS search for all domestic adverse event reports for Plan B in patients less than 18 years of age received since 1999 market approval retrieved 13 cases for analysis. An AERS search for all domestic adverse event reports for Plan B with no age restriction received since March 12, 2008 (data lock point of April 2008 safety review) retrieved 73 cases for analysis.

An analysis of Plan B adverse events using the AERS database, Empirica Signal[®] data mining, and the latest sponsor Periodic Adverse Drug Experience Report (PADER) helped the reviewer evaluate possible new safety signals since the April 2008 safety review. The AERS database did not contain any new fatalities associated with Plan B. The reviewer did not identify any serious, unlabeled adverse events associated with Plan B in patients less than 18 years of age since 1999 market approval. Overall, the reviewer did not identify new safety signals for Plan B that warrant labeling changes. DPV will continue pharmacovigilance activities associated with Plan B.

1 INTRODUCTION

1.1 BACKGROUND

In response to a request from the Office of Executive Secretariat on May 11, 2009, the Adverse Event Reporting System (AERS) database was searched for Plan B adverse event reports. This safety review is an update from a comprehensive review of Plan B completed by the Division of Pharmacovigilance in April 2008.¹ The review evaluates new safety signals associated with Plan B since April 2008 focusing on fatalities, new AERS and data mining results, and serious unlabeled adverse events. The review also includes a summary of all Plan B adverse event reports in patients less than 18 years of age received since 1999 market approval.

Plan B® (levonorgestrel tablets 0.75 mg) is an oral progestin indicated for emergency contraception. The approved dosage regimen is one tablet of Plan B® taken orally as soon as possible within 72 hours after unprotected intercourse. The second tablet should be taken 12 hours after the first dose.²

According to the sponsor's last U.S. Periodic Report covering the period of July 1, 2007 to June 30, 2008, there were approximately ~~————~~ females exposed to Plan B per calendar month, based on the most recent data on the number of Plan B units sold (see Section 3.5).³

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1.2 REGULATORY HISTORY

Plan B is currently the only available dedicated product for emergency contraception in the U.S., containing two levonorgestrel 0.75mg tablets to be taken 12 hours apart. Plan B was approved as a prescription only product on July 28, 1999. In August 2006, Plan B was approved for OTC use in women age 18 and over; it remains a prescription product for women under age 18. Product launch for OTC availability was initiated in November 2006.¹

2 METHODS AND MATERIALS

2.1 INTRODUCTION

Data from AERS, Empirica Signal® data mining (Lincoln Technologies), and the sponsor's 2007-2008 Periodic Adverse Drug Experience Report (PADER) were utilized in this review.

A detailed discussion on the uses of AERS, Empirica Signal® data mining, and PADERs can be found in Appendix 1.

2.2 AERS SEARCH STRATEGY

AERS was searched on May 14, 2009 using the trade name Plan B. The active ingredient levonorgestrel was excluded in the search so as not to capture reports with other products such as Norplant or Mirena.

- 1) The first AERS search included all domestic adverse event reports in patients less than 18 years of age received since 1999 market approval.
- 2) The second AERS search included all domestic adverse event reports received since March 12, 2008 with no age restriction (data lock point from the April 2008 safety review).

Comparatively, the April 2008 review searched the AERS database for any reports since market approval with the suspect drug Plan B listed as the trade name.

2.3 DATA MINING

The Empirica Signal[®] data mining application was searched on May 18, 2009 using the trade name “Plan B” and run name “Trade, Suspect drugs only” and “Trade By Year, Suspect drugs only.” All preferred terms (PTs) with an EB05 \geq 2 were retrieved.

A data mining analysis of the AERS database was performed for this review using Empirica Signal[®] software and the Multi-item Gamma Poisson Shrinker (MGPS)^{6,7} data mining algorithm. MGPS quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted EB05 and EB95 respectively.

Refer to the Appendix 2 for further explanation of Data Mining.

3 RESULTS

3.1 AERS DATA: LESS THAN 18 YEARS OF AGE USING PLAN B

The first AERS search retrieved 13 domestic adverse event reports in patients less than 18 years of age since 1999 market approval. One case retrieved involved the death of a neonate. The cases are summarized below.

Reports in women less than 18 years of age:

Case # 6806560, 15-day Report, October 2008

A 17-year-old female patient who took Plan B for emergency contraception experienced a Tylenol overdose and was hospitalized. Patient recovered.

Case # 6789765, 15-day Report, October 2008

A 17-year-old female patient who took Plan B for emergency contraception experienced a nosebleed and menstrual-like cramping.

Case # 6782254, Periodic Report, August 2008

A 15-year-old female who took Plan B for emergency contraception experienced bright red vaginal bleeding and reported passing two large clots with her vaginal bleeding.

Case # 6782253, Periodic Report, August 2008

A 16-year-old female patient who took Plan B for emergency contraception experienced severe abdominal pains and vomiting after taking the second dose.

Case # 6727731, 15-day Report, August 2008

A 16-year-old female who took Plan B for emergency contraception experienced dizziness and fainting which resolved. The patient stated she fainted after watching her boyfriend “feed a mouse to a snake”.

Case # 6703089, 15-day Report, July 2008

A 15-year-old female patient who took Plan B for emergency contraception experienced dizziness, and non-menses like stomach pain. In addition, she experienced one episode of vomiting blood.

Case # 6673201, 15-day Report, June 2008

A 16-year-old female patient visited the doctor's office for a "Depo" injection for birth control. At the office, the patient's pregnancy test was positive. The report states the patient took Plan B following instruction by her office nurse. The patient subsequently experienced a miscarriage.

Case # 6643262, 15-day Report, April 2008

A 16-year-old female who took Plan B for emergency contraception experienced severe abdominal pain which caused her to faint resulting in a laceration.

Case # 6521034, 15-day Report, December 2007

A 16-year-old female who took Plan B for emergency contraception experienced vomiting and shortness of breath.

Case # 6295990, 15-day Report, April 2007

A 16-year-old female who took Plan B for emergency contraception experienced loss of consciousness for approximately five seconds.

Case # 5733802, Direct Report, April 2003

A 23-year old female (miscoded age) took Plan B for emergency contraception which resulted in a positive pregnancy test.

Case # 3724998, Direct Report, October 2001

A 15-year old female took Plan B for emergency contraception which resulted in a positive pregnancy test.

Neonate Case:

Case # 6530729, 15-day Report, January 2008

This neonate case describes a death of unknown cause 3 days after birth in a premature infant born at five months gestation. Maternal information regards a 31-year-old female patient who took Plan B for emergency contraception. The patient took her first dose of Plan B on an unknown date in 12/2005. On an unspecified date, the patient became pregnant after taking Plan B. No other clinical information was provided and further assessment cannot be made based on this limited information.

In addition to one fatal outcome reported in a neonate, three of thirteen cases had hospitalization as the reported outcome. In the thirteen cases retrieved, the adverse events reported were either addressed in past safety reviews or were unassessable or labeled events. Reports are considered unassessable when the information is insufficient or contradictory.⁸

The second AERS search retrieved 81 domestic adverse event reports since the April 2008 review with 8 duplicate reports resulting in 73 unique cases. Case characteristics are summarized in Table 1.

Table 1 – AERS Case characteristics for Plan B since March 2008 search.	
Search date	05/14/2009
Total # of unique cases	73
Reported Outcomes	Total <ul style="list-style-type: none"> • Life-threatening: 5 • Hospitalization: 7 • Other: 54 • Unknown: 7
Age	<ul style="list-style-type: none"> • Average: 25.1 years • Median: 23.5 years • Range: 18-40 years • Unspecified: 7 cases
Indication	<ul style="list-style-type: none"> • Emergency contraception: 71 • Contraception: 1 • Unspecified: 1
Most frequently reported adverse events (all cases):	<ul style="list-style-type: none"> • Drug exposure During Pregnancy: 41 • Abortion spontaneous: 25 • Unintended pregnancy: 19 (does not include abortion cases) • Ectopic pregnancy: 18 • Uterine hemorrhage: 13 • Vaginal hemorrhage: 11 • Hematemesis: 8 • Menstruation irregular: 8 • Dizziness: 7 • Loss of Consciousness: 6 • Pregnancy after post coital contraception: 6 • Dysmenorrhea: 5 • Fatigue: 5 • Syncope: 5 • Abdominal pain, upper: 4 • Breast Tenderness: 4
Total # of unique cases where conception was reported*	43
Serious Outcomes (conception cases)	Total <ul style="list-style-type: none"> • Life-threatening: 5 • Hospitalization: 5 • Other: 33

* This group includes cases listing abortion (induced, spontaneous or missed), pregnancy (unintended pregnancy, pregnancy, ectopic pregnancy, pregnancy test positive, pregnancy on oral contraceptives) or indicating that drug was ineffective.

Twelve of seventy-three (16%) cases had reported outcomes as life threatening or hospitalization. The average age of Plan B users is 25 years. Emergency contraception was the only specified indication in the cases. In a majority of the cases the lack of information made it difficult for the reviewer to assess a possible association between the event and Plan B. Serious unlabeled

adverse events reported were uterine hemorrhage, hematemesis, loss of consciousness, dysmenorrhea, and syncope; serious unlabeled adverse events *not* addressed in previous safety reviews were uterine hemorrhage and hematemesis (refer to section 4, below, for discussion).

3.2 AERS OVERVIEW-MOST COMMONLY REPORTED TERMS

A total of 81 reports with Plan B as a suspect drug were retrieved from the AERS database. The most commonly reported preferred terms with greater than 2 reports from the May 2009 update are presented in **Table 2** below comparing data from the April 2008 review. See Appendix 3 for most commonly reported preferred terms with a count of 1 and 2 reports.

Table 2. Most Commonly Reported Preferred Terms in Plan B Reports in the AERS Database comparing data from the April 2008 review.

Preferred Term (PT)	N	% of Total* (N=139)	N	% of Total* (N=81)	Location in Label or Comment
	April 2008 data		May 2009 data		
Vaginal Haemorrhage	28	20.1	11	13.5	WARNINGS – Effects on menses
Unintended Pregnancy	19	13.7	19	23.4	Clinical Studies
Nausea	17	12.2	9	11.1	Adverse reactions
Abdominal Pain	15	10.8	16	19.7	Adverse reactions
Ectopic Pregnancy	15	10.8	18	22.2	WARNINGS – Ectopic Pregnancies
Vomiting	12	8.6	3	3.57	Adverse reactions
Dizziness	11	7.9	7	8.6	Adverse reactions
Metrorrhagia	11	7.9	4	4.76	WARNINGS – Effects on menses
Drug Exposure During Pregnancy	10	7.2	41	50.6	Clinical Studies
Abortion Spontaneous	9	6.5	25	30.8	Unlabeled
Menstruation Irregular	8	5.8	8	9.8	WARNINGS – Effects on menses
Fatigue	7	5.0	5	6.1	Adverse reactions
Oligomenorrhoea	7	5.0	No reports		WARNINGS – Effects on menses
Pelvic Pain	7	5.0	9	11.1	Unlabeled
Syncope	7	5.0	5	6.1	Unlabeled
Complications Of Maternal Exposure To Therapeutic Drugs	6	4.3	No reports		Unlabeled
Diarrhoea	6	4.3	No reports		Adverse Reactions
Drug Ineffective	6	4.3	No reports		Clinical Studies
Loss Of Consciousness	6	4.3	6	7.4	Unlabeled
Headache	5	3.6	3	3.57	Adverse reactions
Abdominal Pain Upper	4	2.9	4	4.9	Adverse reactions
Pregnancy After Post Coital Contraception	4	2.9	6	7.4	Clinical Studies
Uterine Haemorrhage**			13	16.0	Unlabeled
Haematemesis**			8	9.8	Unlabeled
Dysmenorrhoea**			5	6.1	Unlabeled
Breast Tenderness**			4	4.9	Labeled

* % of Total: the number of occurrences of PTs in the cases over the total number of reports in the individual case series; sum does not equal 100%

**New Preferred Terms identified by the reviewer since April 2008 review

3.3 AERS REPORTS WITH FATAL OUTCOMES

Since 1999 market approval, the AERS database contains four fatal outcomes reported in association with Plan B. Two of these reports are duplicates resulting in two fatal outcome reports. No new fatalities have been reported since the April 2008 review. The neonatal case was unassessable due to lack of information.

3.4 DATA MINING

Table 3 displays comparative data mining results from the April 2008 safety review.

Table 3. Data mining Scores (EB05 >2) for Plan B (Trade Name) April 2008 versus May 2009

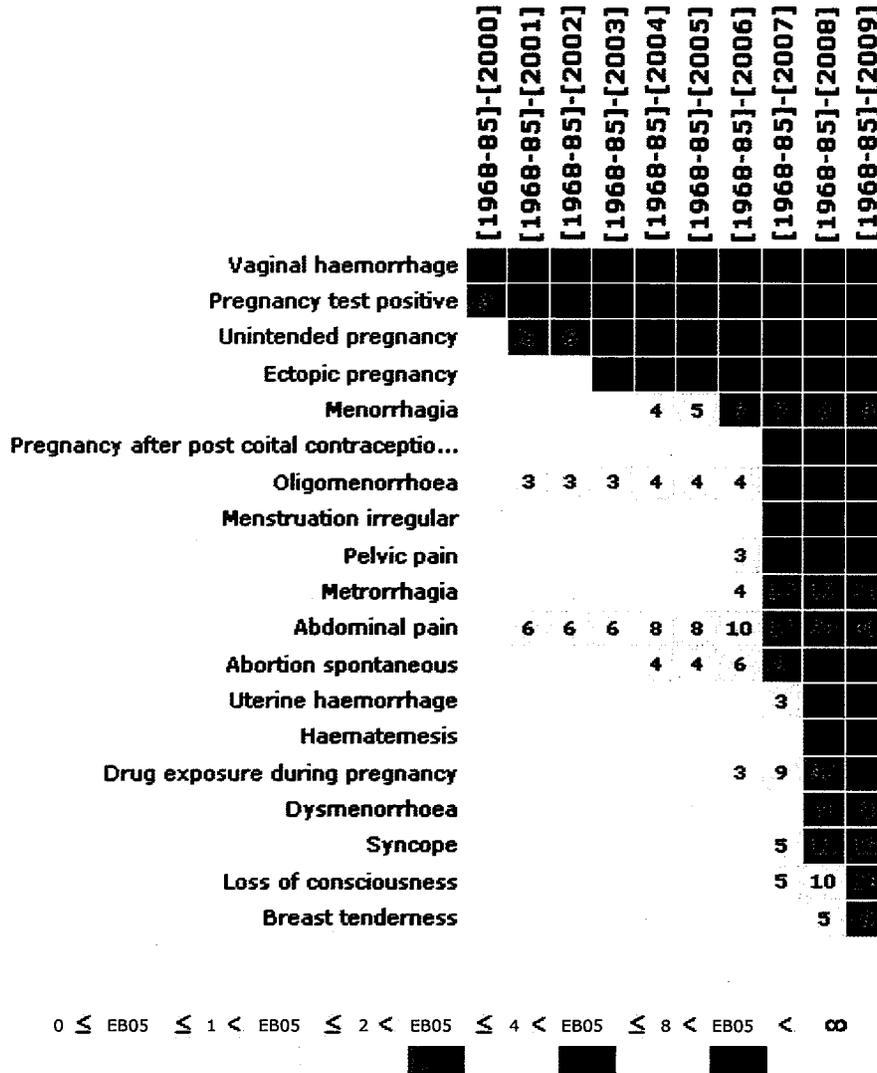
Preferred Term (PT)	N	EB05	N	EB05	Location in Label or Comment
	April 2008 data		May 2009 data		
Pregnancy test positive	7	47.0	7	31.8	Clinical Studies
Pregnancy after post coital contraception	4	35.2	10	129.7	Clinical Studies
Ectopic pregnancy	13	32.7	30	51.8	WARNINGS – Ectopic Pregnancy
Vaginal haemorrhage	27	22.4	37	9.6	WARNINGS – Effects on menses
Unintended pregnancy	18	16.0	37	26.3	Clinical Studies
Oligomenorrhoea	7	14.5	7	5.2	WARNINGS – Effects on menses
Menstruation irregular	8	5.3	16	14.4	WARNINGS – Effects on menses
Pelvic pain	6	4.0	15	12.1	Unlabeled
Metrorrhagia	11	2.7	14	2.4	WARNINGS – Effects on menses
Menorrhagia	7	2.5	9	2.2	WARNINGS – Effects on menses
Abdominal pain	14	2.1	31	3.3	Adverse Reactions
Abortion spontaneous	9	2.0	33	6.1	Unlabeled
Uterine haemorrhage*			16	38.6	Unlabeled
Haematemesis*			11	11.6	Unlabeled
Drug exposure during pregnancy*			50	4.6	Clinical trials
Dysmenorrhoea*			8	3.5	Unlabeled
Syncope*			12	2.5	Unlabeled-addressed in April 2008 review
Loss of consciousness*			13	2.3	Unlabeled-addressed in April 2008 review
Breast tenderness*			6	2.1	Adverse Reactions

*New Preferred Terms identified by the reviewer with EB05>2 since the April 2008 review

Graph 1 below illustrates data mining safety signals with Plan B. The rows list the Preferred Terms (PTs) or single medical concepts and the columns list the year of adverse events. The numbers in the tiles indicate the number of adverse event reports and the colors indicate the various EB05 scores. The darker the tiles, the higher the EB05 score. Typically, EB05 scores greater than 2 indicate a safety signal. Additional restrictions for this graph were N values of at least 3 reports and EB05 scores of at least greater than 2.

Graph 1. 2009 Data Mining results for Plan B since market approval

Listing Preferred Terms with EB05 scores >2

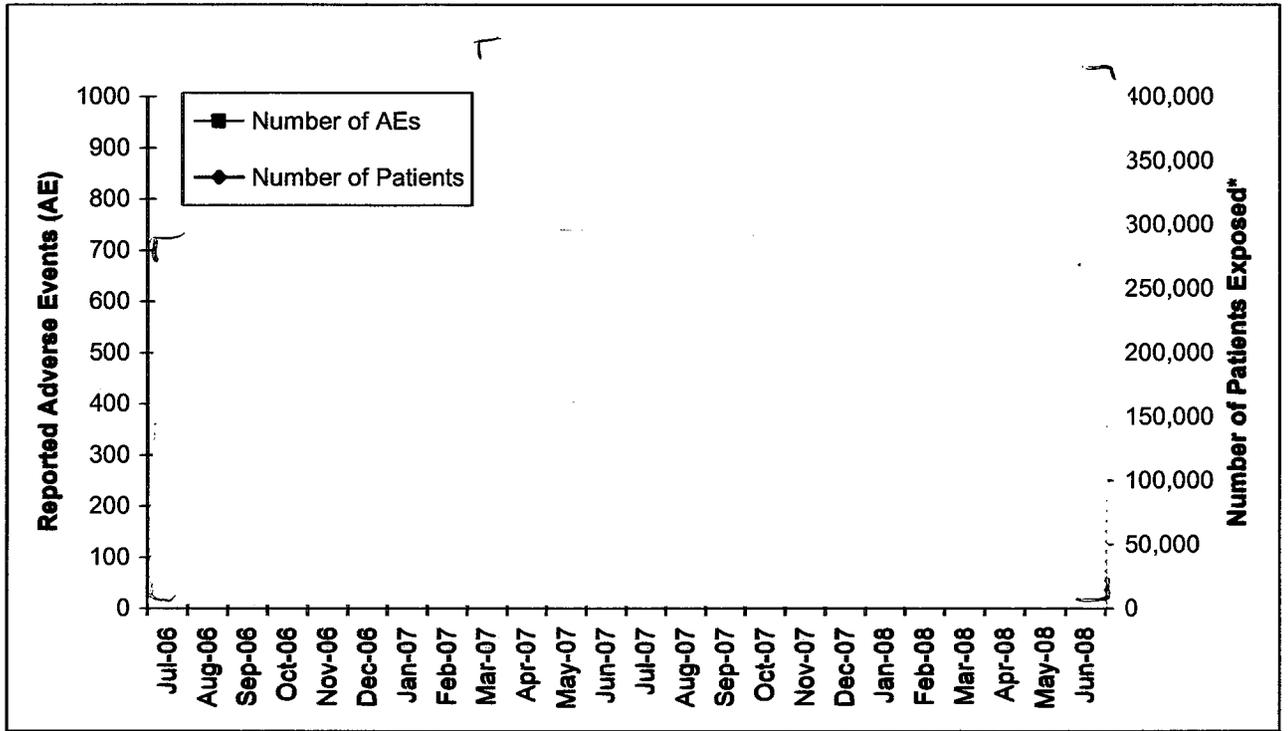


Graph 1 displays nineteen Preferred Terms with an EB05 score > 2 for Plan B since 1999 market approval. In other words, there are nineteen possible safety signals identified from the graph.

3.5 SPONSOR'S PERIODIC ADVERSE DRUG EXPERIENCE REPORT (PADER)

Table 5 and 6 are results from the sponsor's latest PADER from July 1, 2007 to June 30, 2008.

Figure 1. Sponsor's Data of Patient Exposure and Post-marketing Adverse Event Reports from July 1, 2006 through June 30, 2008



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* Sponsor's estimate of patient exposure based on the number of Plan B units sold

In general, Figure 1 shows the number of patients exposed to Plan B per month has increased while the number of serious and non-serious adverse event cases per month has somewhat stabilized since March 2007.

Table 5. Sponsor's Summary of Categorization of Post-marketing Adverse Event Reports Received from July 1, 2007 through June 30, 2008

	Total # Reports	Serious		Non-Serious	
		Expected	Unexpected	Expected	Unexpected
Health Care Professionals	47	2	5	28	12
Non-Health Care Professionals	15,385	16	46	11,735	3,588

	Total # Reports	Serious		Non-Serious	
		Expected	Unexpected	Expected	Unexpected
Total	15,432	18	51*	11,763	3,600

*The 51 Serious, Unexpected reports submitted to the FDA were included in the AERS data analysis.

Adverse Event Preferred Term	Number of Reports
Gastrointestinal disorders	
Abdominal pain	632
Nausea	1275
Vomiting	603
General disorders and administration site conditions	
Fatigue	486
Nervous system disorders	
Dizziness	515
Headache	562
Reproductive system and breast disorders	
Dysmenorrhea	653
Menstruation irregular	5505
Oligomenorrhoea	533
Pelvic pain	733
Total	11,497

4 DISCUSSION

An analysis of Plan B adverse events using the AERS database, Empirica Signal[®] data mining, and the latest sponsor PADER helped the reviewer evaluate possible new safety signals since the April 2008 safety review. When evaluating postmarketing adverse event reports it is important to note that while the databases can identify potential safety signals, there is no certainty that these drugs caused the reported reactions. The AERS database did not contain any new fatalities associated with Plan B in the U.S. The reviewer did not identify any serious, unlabeled adverse events in patients less than 18 years of age since 1999 market approval in the U.S.

The reviewer identified uterine hemorrhage, hematemesis, drug exposure during pregnancy, dysmenorrhea, syncope, loss of consciousness, and breast tenderness as possible new safety signals according to data mining. New possible serious unlabeled adverse events associated with Plan B not addressed in the April 2008 review were uterine hemorrhage and hematemesis. According to data mining, Graph 1 shows uterine haemorrhage (N=16) and hematemesis (N=11)

7 REFERENCES

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4. Accessed on inside.fda.gov website on May 19, 2009. Powerpoint presentation: Safety Reporting. Easley, Olivia, MD, Medical Officer, DRUP.
5. **Using the FDA's Adverse Event Reporting System (AERS) in Postmarketing Surveillance.** Weaver JP, Safety Evaluator. DSaRM Advisory Committee. May 18, 2005.
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8. The use of the WHO-UMC system for standardized case causality assessment [monograph on the Internet]. Uppsala: The Uppsala Monitoring Centre; 2005. Available from: <http://www.who-umc.org/graphics/4409.pdf>.

APPENDIX 1

AERS is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The Empirica Signal[®] data mining uses computerized algorithms to identify hidden patterns of **associations or unexpected occurrences ('signals') in large databases**. The safety reviewer can then evaluate these signals for intervention as appropriate. In accordance with FDA regulations, the sponsor is required to submit a PADER quarterly for 3 years from the date of approval of the NDA, then annually. The PADER presents a summary of adverse events submitted in 15-day reports and other adverse events not reported in 15-day format such as non-serious labeled and unlabeled and serious labeled events. In addition, the sponsor notifies the FDA if any actions were taken since the last report such as labeling changes or studies initiated. The PADER does not contain reports from foreign marketing experience, scientific literature or post-marketing studies.^{1,4}

The FDA's data mining and AERS databases are useful tools to help the reviewer assess possible safety signals, yet there are limitations to the data. Data mining systematically "mines" AERS using mathematical tools to identify higher-than-expected frequency of product-event combinations. Data mining is a tool for hypothesis generation to help the reviewer identify potential new safety signals. It does not replace expert clinical case review and interpretation. Once a data mining signal is identified, the reviewer should assess the cases in AERS.⁵ Agency operating procedures determine which adverse event reports are entered into the AERS database based on the report type: 15-day alert report, direct report from a consumer or healthcare professional, or non-serious adverse event report from the pharmaceutical sponsor's Periodic reports. In addition, non-serious adverse event reports from the sponsor's Periodic reports may or

may not be entered into the AERS database based on time on market and other factors; for instance, a sponsor may make a waiver request for submission of non-serious and labeled events to be substituted by a tabulation of these reports in the periodic report.¹ AERS limitations include duplicate reporting; extensive underreporting; variability in the quality of the reports; reporting biases; an unknown number of events in the population and number of exposed patients; and difficulty in attributing events with a high background rate, confounders, and long latency period.⁵

APPENDIX 2

EBGM values indicate the strength of the reporting relationship between a particular drug and event, as reported in AERS. For example, if EBGM=10 for a drug-event combination, then the drug-event occurred 10 times more frequently in the database than statistically expected when **considering all other drugs and events in AERS database as a background, the “expected.”** A drug-event combination having an EB05 ≥ 2 indicates 95% confidence that this drug-event combination occurs at least twice the expected rate when considering all other drugs and events in the database. A drug-event combination having an EB05 > 1 indicates 95% confidence that this drug-event combination occurs at least at a higher-than-expected rate considering all other drugs and events in the database.

The higher the EBGM score (and accompanying EB05, EB95 confidence intervals) for a particular drug-event, the higher the association is between that drug and event, given the **database being analyzed. Note that this “association” is a result of the relative reporting for various events among all drugs in the database.** The scores discussed in this review provide an indication of the association of adverse events with **Plan B**, given the data analyzed. The exact degree of this association (in all patients exposed to the drug worldwide), however, cannot be elicited from an MGPS data mining analysis alone, because obviously the association scores **(EB05 values) from such an analysis are generated from the specific database analyzed—in this case AERS** which consists of spontaneous adverse events reports. It is also important for the reader to understand that an elevated EBGM or EB05 score of association for a particular drug-event combination does not prove causality or an increased relative risk of that drug-event. Similarly, the absence of an elevated EBGM or EB05 score for a drug-event cannot be interpreted as a definite lack of toxicity for that drug-event. Finally, reporting and detection biases can occur in AERS and effects of concomitant illnesses or therapy cannot be fully controlled in data mining analyses using MGPS. Because of the spontaneous nature of reporting, the results of this analysis should not be interpreted as a formal comparison of treatment groups or of their relative risks.

APPENDIX 3

FDA-AERS Standard Report: All Preferred Terms in Cases resulting in count of one PT (N=65)

Abdominal discomfort, Abdominal Distention, Abnormal Withdrawal Bleeding, Abortion Missed, Abortion of Ectopic Pregnancy, Abortion Threatened, Acne, Affect Lability, Alanine Aminotransferase Increased, Alcohol Use, Alopecia, Anorexia, Anxiety, Aspartate Aminotransferase Decreased, Asthenia, Bipolar Disorder, Blood Alkaline Phosphatase Increased, Blood Bilirubin Increased, Blood Urine Present, Breast Discharge, Breast Pain, Breast Swelling, Candidiasis, Chest Pain, Cholelithiasis, Condition Aggravated, Dizziness Postural, Drug Administration Error, Dyspepsia, Dysuria, Facial Bones Fracture, Fallopian Tube Disorder, Fallopian Tube Perforation, Fear of Pregnancy, Feeling Hot, Haemorrhage, Hallucination (Visual), Memory Impairment, Mood Altered, Nightmare, Oophorectomy, Overdose, Pain in Extremity, Palpitations, Pelvic Neoplasm, Photopsia, Pregnancy on Contraceptive, Pregnancy Test Urine Positive, Pyrexia, Retching, Scar, Skin Laceration, Stress, Therapeutic Response

Delayed, Thrombosis, Treatment Failure, Twin Pregnancy, Unevaluable Event, Uterine Cervical Pain, Vaginal Discharge, Vision Blurred, Visual Impairment, Vulvovaginal Burning Sensation, Vulvovaginal Pain, Vulvovaginal Pruritis.

FDA-AERS Standard Report: All Preferred Terms in Cases resulting in count of two PTs (N=14)

Abdominal Pain Lower, Abortion Induced, Back Pain, Blood Pressure Decreased, Convulsion, Dyspnoea, Epistaxis, Feeling Abnormal, Genital Haemorrhage, Maternal Drugs Affecting Foetus, Menorrhagia, Menstruation Delayed, Pregnancy On Oral Contraceptive, Tremor.

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/s/

Mark Miller
6/19/2009 09:30:16 AM
DRUG SAFETY OFFICE REVIEWER

Melissa Truffa
6/19/2009 09:37:43 AM
DRUG SAFETY OFFICE REVIEWER

Robert M Boucher
6/19/2009 09:40:51 AM
MEDICAL OFFICER

Gerald DalPan
6/19/2009 03:32:15 PM
DRUG SAFETY OFFICE REVIEWER



OTC Drug Labeling Review ADDENDUM

Office of Nonprescription Products (ONP)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-998

Submission Date: June 9, 2009

Type of Submission: Amendment to a Pending Application: Response to Request for Information - Labeling

Sponsor: Duramed Research Inc.

Drug Product: Plan B® One-Step Emergency Contraceptive

Active Ingredient: •Levonorgestrel tablet, 1.5 mg in each tablet

Indications: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 1 tablet, 1.5 mg levonorgestrel in each tablet, which is one dose.

Review Date: June 20, 2009

Reviewer: Arlene Solbeck
IDS, DNRD

Project Manager: Leah Christl
ADRA, ONP

Background

Reference is made to the label review for this submission that was placed in DFS on 6/18/09. In that review, we recommended that the sponsor revise the information on Page 17 of the Consumer Information Leaflet about what to do if vomiting occurs after taking the product. We told them to revise the vomiting statement to "If you vomit within 2 hours of taking the medication, call a healthcare professional to discuss whether to repeat the dose". After further consideration, we are revising our recommendation and

are asking the sponsor to revise the statement to read as follows: If you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose.

Reviewer's Recommendation

Based on further discussion with DNCE's MOs, we recommend that the statement about vomiting on Page 17 of the Consumer Information Leaflet be revised to read as follows:

"If you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose."

Arlene Solbeck
IDS
DNRD

Marina Chang
IDS Team Leader
DNRD

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/s/

Arlene Solbeck
6/19/2009 01:45:59 PM
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Marina Chang
6/19/2009 01:47:50 PM
INTERDISCIPLINARY



OTC Drug Labeling Review

Office of Nonprescription Products (ONP)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-998

Submission Date: June 9, 2009

Type of Submission: Amendment to a Pending Application: Response to Request for Information - Labeling

Sponsor: Duramed Research Inc.

Drug Product: Plan B® One-Step Emergency Contraceptive

Active Ingredient: •Levonorgestrel tablet, 1.5 mg in each tablet

Indications: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 1 tablet, 1.5 mg levonorgestrel in each tablet, which is one dose.

Review Date: June 15, 2009

Reviewer: Arlene Solbeck
IDS, DNRD

Project Manager: Leah Christl
ADRA, ONP

Background

Plan B® is emergency contraception, a backup method of birth control. Plan B® can reduce the risk of pregnancy after unprotected sex (i.e. if a regular birth control method fails or after sex without birth control). Plan B® contains a concentrated dose of levonorgestrel, a synthetic hormone used in birth control pills for over 35 years. FDA approved Plan B® for prescription use on July 28, 1999 under NDA 21-045. On April 16, 2003, the former sponsor (Women's Capital Corporation) submitted an NDA to

switch Plan B One-Step from prescription status to OTC. FDA approved the supplement on August 24, 2006 for OTC sale to consumers 18 years of age and older and for Rx sale for consumers under the age of 18 years.

On January 24, 2006, the current sponsor (Duramed) submitted a new drug application (NDA 21-998) for a single dose levonorgestrel tablet, 1.5 mg, to be taken within 72 hours of unprotected sexual intercourse. The application received an approvable action on November 22, 2006 pending the submission of revised labeling necessary to market this one tablet dose of levonorgestrel 1.5 mg OTC for women aged 18 years and above, and as a prescription product for women 17 years and younger. On January 9, 2009 the sponsor submitted revised carton labels and a draft consumer information leaflet for the OTC product for consumers 18 years of age and over and a draft Rx label for the Rx product for consumers 17 years of age and under. We sent the sponsor labeling comments for the OTC product on May 29, 2009. This submission addresses those labeling comments, and, in addition, revises the labeling to change the population for Plan B One-Step from _____

_____ to "OTC for consumers 17 or older and by prescription for women age 16 or younger." This labeling also revises the proprietary name of the drug to Plan B One-Step. On May 13, 2009, FDA granted approval for the proprietary name of the drug as Plan B One-Step.

For this current submission, the sponsor (Duramed) submitted for review:

1. revised carton labels for Plan B One-Step retail pack ar. _____
2. a draft consumer information leaflet for the OTC product for consumers 17 years of age and over.
3. a draft Rx label for the Rx product for consumers 16 years of age and under.

This label review covers the OTC cartons and consumer information leaflet.

I. Reviewer's Comments

On May 13, 2009, the sponsor received approval to revise the proprietary name of this drug to Plan B One-Step. Therefore, anywhere the prior labeling stated the name of the product as Plan B One-Step was revised to read "Plan B One-Step". This is the acceptable name of the product.

The other comments for the proposed Plan B One-Step labels that were sent to the sponsor were addressed as follows:

A. Principal Display Panel (PDP)

1. We recommend a flag on the PDP of the carton for the Plan B One-Step product which announces that this is a new dosage form. We recommend that the flag should be removed after 6 months of marketing.

Sponsor's Response: Sponsor included a statement on the PDP that states "NEW! Now only ONE pill". This is acceptable.

2. If both the 0.75 mg dual pack and the 1.5 mg single dose products will overlap each other in the marketplace, we recommend that the potency in the statement of identity look more prominent and distinctly different for each product.

Sponsor's Response: Sponsor has made the potency look different for each product. They are acceptable.

3. The established name on the PDP should read "(Levonogestrel) tablet 1.5mg", not _____

b(4)

Sponsor's Response: Sponsor changed the established name as requested to "(Levonogestrel) tablet 1.5mg".

4. Additional change: sponsor revised the statement on the upper right corner of the PDP from _____ to "Rx only for age 16 or younger" to reflect the change in the OTC population. This is acceptable.

b(4)

B. Drug Facts

5. Under "Directions", for the second bulleted statement which begins _____, insert the word "tablet" after the word "take" for clarity (i.e., "take tablet as soon as possible.....").

b(4)

Sponsor's Response: Sponsor made this change and statement is acceptable.

6. The bulleted statement under "Directions" (for Plan B dual pack) which states "prescription only for age 17 and under. If age 17 or under, see a healthcare professional." was revised (shortened) for Plan B One-Step to read _____ We recommend that the original statement be reinstated for clarity.

b(4)

Sponsor's Response: The sponsor made several changes to "Directions" in response to our request and also to address the new OTC population. First, the sponsor revised the first bulleted statement under "Directions" from _____ to "women 17 years of age and over:" to reflect the change in the OTC population. This is acceptable. The sponsor also revised the third bulleted statement under "Directions" to read: _____

b(4)

_____ This incorporates the change we asked for, and also the change in age for the OTC population. This is acceptable.

7. Under "Other information", the tamper-evident feature statement which begins _____ should be revised to read "tablet is enclosed..." since Plan B One-Step is a single dose product.

b(4)

Sponsor's Response: The sponsor made the change from _____ to "tablet". This is acceptable.

b(4)

C. Consumer Information Leaflet (CIL)

8. Cover. The word _____ should be inserted before _____ in the statement "_____".

b(4)

Sponsor's Response: Sponsor inserted the word _____ before _____ on the cover. This is acceptable.

9. The sponsor renumbered all the pages of the CIL. There were 17; now there are 24. This is acceptable.

10. (Former) Page 11; current page 17: Under the overdose warning, we recommend that the sponsor insert the Poison Control Center telephone number.

Sponsor's Response: On Page 17, sponsor added the Poison Control Center telephone number. This is acceptable.

11. (Former) Page 11; current page 17: Revise the very last sentence on page 11 to read "_____". It looks like some words were left out because it currently reads "_____".

b(4)

Sponsor's Response: Sponsor made two revisions in this "Directions" section. First, they revised the heading for the directions to read "_____". rather than "_____". Second, they revised the very last sentence to read "_____".

b(4)

_____ This responds to our request and also changes the age to reflect the new OTC population. Both changes are acceptable.

12. Current page 16: Sponsor revised the side effects from using the product and eliminated "_____". without prior approval. We asked the sponsor why they did this in a telecon on June 15, 2009 and they said this was an update based on recent clinical trials using Plan B One-Step. Therefore, this change is acceptable.

b(4)

13. Current page 17: Sponsor revised the comment about vomiting from "_____". to read "_____".

b(4)

This is a different vomiting statement than what

is in the Plan B (two dose) CIL which reads " _____"

b(4)

It is not clear whether it is acceptable that the leaflets do not have the same directions for what to do is vomiting occurs. We recommend that the vomiting statement for Plan B-One-Step be changed to read: "If you vomit within 2 hours of taking the medication, call a healthcare professional to discuss whether to repeat the dose." as per DNCE's MO's email dated 6/17/09.

14. (Former) Page 12; current page 18: Under "What should I do if I have questions about Plan B®" _____, put a period at the end of the statement that begins "If you have questions.....".

b(4)

Sponsor's Response: Sponsor put a period at the end of the statement. This is acceptable.

15. (Former) Page 12; current page 18: Under "Other information", revise first sentence from ' _____' to "Tablet is enclosed in a blister seal."

b(4)

Sponsor's Response: Sponsor revised _____ to "tablet". This is acceptable.

b(4)

16. (Former) Page 12, current page 18: Put a period after the storage temperature statement.

Sponsor's Response: Sponsor put a period after the storage temperature statement.

II. Reviewer's Recommendations

The changes and revisions that the sponsor made, both in response to our comments and in regard to changing the proprietary product name of the drug and also the OTC population age and Rx population age, are acceptable with one exception:

- Current page 17 of the CIL: the sponsor needs to revise the vomiting statement to read "If you vomit within 2 hours of taking the medication, call a healthcare professional to discuss whether to repeat the dose."

Arlene Solbeck
IDS
DNRD

Marina Chang
IDS Team Leader
DNRD

27 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

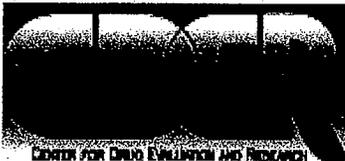
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/s/

Arlene Solbeck
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Marina Chang
6/17/2009 03:16:22 PM
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Ready for DFS
4/22/09



OTC Drug Labeling Review

Office of Nonprescription Products (ONP)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 21-998

Submission Date: January 9, 2009

Type of Submission: New Drug Application (NDA) for a single dose of 1.5 mg levonorgestrel

Sponsor: Duramed Research Inc.

Drug Product: Plan B® — Emergency Contraceptive **b(4)**

Active Ingredient: •Levonorgestrel tablet, 1.5 mg in each tablet

Indications: •reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Stock Keeping Units: 1 package contains 1 tablet, 1.5 mg levonorgestrel in each tablet, which is one dose.

Review Date: April 20, 2009

Reviewer: Arlene Solbeck
IDS, DNRD

Project Manager: Leah Christl
ADRA, ONP

Background

Plan B® is emergency contraception, a backup method of birth control. Plan B® can reduce the risk of pregnancy after unprotected sex (i.e. if a regular birth control method fails or after sex without birth control). Plan B® contains a concentrated dose of levonorgestrel, a synthetic hormone used in birth control pills for over 35 years. FDA approved Plan B® for prescription use on July 28, 1999 under NDA 21-045. On April 16, 2003, the sponsor (Women's Capital Corporation) submitted an NDA to switch Plan

B® from prescription status to OTC. FDA approved the supplement on August 24, 2006 for OTC sale to consumers 18 years of age and older and for R_x sale for consumers under the age of 18 years.

On January 24, 2006, the current sponsor (Duramed) submitted a new drug application (NDA 21-998) for a single dose levonorgestrel tablet, 1.5 mg, to be taken within 72 hours of unprotected sexual intercourse. The application received an approvable action on November 22, 2006 pending the submission of revised labeling necessary to market this one tablet dose of levonorgestrel 1.5 mg OTC for women aged 18 years and above, and as a prescription product for women 17 years and younger.

For this current submission, the sponsor (Duramed) submitted for review:

1. revised carton labels for Plan B® ~~_____~~ Dual Label Pack and Plan B® ~~_____~~ b(4)
2. a draft consumer information leaflet for the OTC product for consumers 18 years of age and over
3. a draft R_x label for the R_x product for consumers 17 years of age and under.

This label review covers the OTC cartons and consumer information leaflet.

I. Reviewer's Comments

Comments and recommendations for the proposed Plan B® ~~_____~~ labels are as follows: b(4)

A. Principal Display Panel (PDP)

- We recommend a flag on the PDP of the carton for the Plan B® ~~_____~~ product which announces that this is a new dosage form. We recommend that the flag should be removed after 6 months of marketing. b(4)
- If both the 0.75 mg dual pack and the 1.5 mg single dose products will overlap each other in the marketplace, we recommend that the potency in the statement of identity look more prominent and distinctly different for each product.
- The established name on the PDP should read "(Levonogestrel) tablet 1.5mg", not ~~_____~~ b(4)
- The NDC printed on the carton should agree with the number printed on the PI for R_x labeling.

B. Drug Facts

- Under "Directions"; for the second bulleted statement which begins ~~_____~~ insert the words "one tablet" after the word "take" for clarity (i.e., "take one tablet as soon as possible....."). b(4)

b(4)

- The bulleted statement under "Directions" (for Plan B®) which states "prescription only for age 17 and under. If age 17 or under, see a healthcare professional." was revised (shortened) for Plan B® to read "_____". We recommend that the original statement be reinstated for clarity. b(4)
- Under "Other information", the tamper-evident feature statement which begins "_____ should be revised to read "tablet is enclosed..." since Plan B® is a single dose product. b(4)

C. Consumer Information Leaflet (CIL)

This CIL was compared with the CIL for Plan B®. It is identical to the approved CIL with the following exceptions:

- Cover. The word "_____" should be inserted before "_____" in the statement "_____". b(4)
- Page 1. A new section called "What Plan B_____ isn't." was added to the leaflet.
- Page 2. Under "When is the appropriate time to use Plan B_____" the original Plan B® leaflet said "_____". The new leaflet says "_____". b(4)
- Page 11. Under the overdose warning, we recommend that the sponsor insert the Poison Control Center telephone number.
- Page 11. Revise the very last sentence on page 11 to read "_____". It looks like some words were left out because it currently reads "_____". b(4)
- Page 12. Under "What should I do if I have questions about Plan B®" _____ put a period at the end of the statement that begins "If you have questions.....".
- Page 12. Under "Other information", revise first sentence from "_____ to "Tablet is enclosed in a blister seal." b(4)
- Page 12. Put a period after the storage temperature statement.

II. Reviewer's Recommendations

The sponsor's **must** make the following revisions to the label before this supplement can be approved, and submit carton and consumer information leaflet for our review and comment prior to the PDUFA action date:

A. PDP

- The established name on the PDP should read "(Levonogestrel) tablet 1.5mg", not "_____". b(4)

B. Drug Facts

b(4)

- Under "Directions", for the second bulleted statement which begins "_____"; insert the words "one tablet" after the word "take" for clarity (i.e., "take one tablet as soon as possible.....").
- The bulleted statement under "Directions" (for Plan B®) which states "prescription only for age 17 and under. If age 17 or under, see a healthcare professional." was revised (shortened) for Plan B® to read "_____". We recommend that the original statement be reinstated for clarity.
- Under "Other information", the tamper-evident feature statement which begins "_____ should be revised to read "tablet is enclosed..." since Plan B® is a single dose product.

b(4)

b(4)

C. CIL

- Cover. The word "_____ should be inserted before "_____ in the statement "_____".
- Page 11. Revise the very last sentence on page 11 to read "If under 17 years of age, see a healthcare professional." It looks like some words were left out because it currently reads "_____".
- Page 12. Under "What should I do if I have questions about Plan B®", put a period at the end of the statement that begins "If you have questions.....".
- Page 12. Under "Other information", revise first sentence from "_____ to "Tablet is enclosed in a blister seal." because this is a one-dose product.
- Page 12. Put a period after the storage temperature statement.

b(4)

b(4)

We recommend that the sponsor make the following changes to the labels. The sponsor can include these changes in the labels that they submit to FDA for review and comment prior to the PDUFA action date.

A. PDP

- Put a flag on the PDP of the carton for the Plan B® product which announces that this is a new dosage form. The flag should be removed after 6 months of marketing.
- If both the 0.75 mg dual pack and the 1.5 mg single dose products will overlap each other in the marketplace, we recommend that the potency in the statement of identify look more prominent and distinctly different for each product.

b(4)

B. Consumer Information Leaflet

- Page 11. Under the overdose warning, sponsor should insert the Poison Control Center telephone number.

Additional comments to the project manager:

- Please check with clinical to ensure that there are no additional revisions to the labeling before communicating to the sponsor. This review was completed prior to the completion of the clinical review.
- Inform the sponsor that additional labeling revisions may be required pending the completion of the clinical reviews.
- We are waiting to hear whether there will be an age change for the OTC marketing of this product. If there is, the sponsor will be required to revise the age related statements on the labels.

Arlene Solbeck
IDS
DNRD

Marina Chang
IDS Team Leader
DNRD

21 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Arlene Solbeck
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Marina Chang
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**Office of Surveillance
and Epidemiology**

MEMO

To: Scott Monroe, M.D.
Acting Director, Division of Reproductive and Urologic Products
HFD-580

Through: Alina R. Mahmud, R.Ph., M.S., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; White Oak Bldg. 22, Mail Stop 4447

From: Jinhee L. Jahng, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; White Oak Bldg. 22, Mail Stop 4447

Date: October 17, 2006

Re: OSE Review #2006-616
_____ Plan P _____ Plan B _____ and _____ b(4)
NDA#: 21-998

This memorandum is in response to a October 16, 2006 request from your Division for a labeling review for the proprietary names _____ Plan B _____ 'Plan B _____ and _____ Since the sponsor withdrew their request to review the name, _____ DMETS did not review this name. In a review dated August 10, 2006 (OSE Review #'s 06-0101, 2006-16, 2006-24, and 2006-25), we stated that we do not recommend Plan P _____ Plan B _____ and _____

b(4)

We have further been notified that the sponsor may change the labeling altogether but are requesting that we review their previously submitted labels and labeling. If and when revised labels and labeling have been submitted, please forward them to DMETS for further review.

In the review of the carton and insert labeling of "_____", DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement, which might minimize user error.

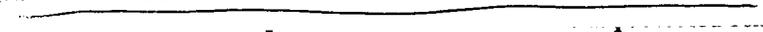
b(4)

1. GENERAL COMMENT

Revise the labels and labeling so that the stated name, _____ is replaced with the proprietary name approved with this application.

b(4)

2. **CARTON LABELING**

- a. See **GENERAL COMMENT**.
- b. The purple font color used for the text, contrasted with the bluish background color is difficult to read. Revise the background color to improve the readability or use a darker font color so that the background color is contrasted with the color used for the text.
- c. The product strength and dosage form "tablet" is printed in smaller font beneath the established name and is difficult to read. Increase the prominence of the strength and dosage form so that it appears as the same size as "Levonorgestrel".
- d. The strength appears with the proprietary and established name. In its current presentation, the "1.5 mg" looks as if it is part of the proprietary name. Revise the labeling so that the strength appears immediately following the established name, not the proposed proprietary name.
- e. A graphic design is present on the label. This graphic item appears more prominent than the proprietary and established names, whereas the names and strength should appear most prominently on the labels and labeling. Therefore, we recommend removing this graphic design or at a minimum, decreasing the size so that the proprietary and established names and strength are the most prominent information on the labels and labeling.
- f. A purple oval-like circle appears on the back panel of the carton labeling with the instructions,  (see picture below). It is not apparent what the information included in this circle is, thus we recommend including a "Usual dosage" statement immediately preceding the administration instructions.

b(4)



b(4)

3. **INSERT LABELING**

The proposed proprietary name has been omitted from the insert labeling. Revise to include this name in the labeling when available.

If you have any other questions or need clarification, please contact the Medication Errors Project Manager, Diane Smith, at 301-796-0538.

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/s/

Jinhee Jahng
10/20/2006 01:37:07 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
10/20/2006 01:44:46 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/20/2006 02:03:56 PM
DRUG SAFETY OFFICE REVIEWER

Office of Surveillance
and Epidemiology

MEMO

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Products
HFD-580

Through: Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support,
Office of Surveillance and Epidemiology
HFD-420; White Oak Bldg. 22, Mail Stop 4447

From: Jinhee L. Jahng, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support,
Office of Surveillance and Epidemiology
HFD-420; White Oak Bldg. 22, Mail Stop 4447

Date: August 10, 2006

Re: OSE Review #'s 06-0101, 2006-16, 2006-24, and 2006-25
Plan B, Plan P and , respectively
NDA#: 21-998

This memorandum is in response to an March 21, 2006 and August 7, 2006 request from your Division for a review of the proprietary names ' Plan P , 'Plan P and ' respectively. The Sponsor withdrew their proprietary name. Therefore, DMETS will not be reviewing this proposed proprietary name from a safety perspective. b(4)

Additionally, upon the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising and Communications (DDMAC) found the proprietary name 'Plan B acceptable from a promotional perspective, however, they did not recommend the use of the proposed proprietary names, 'Plan B and ' because they minimize the potential risks associated with the drug product. DDMAC specifically states the following: b(4)

DDMAC objects to the proposed trade names Plan B and because they minimize the potential risks associated with the drug product. While the proposed trade names may convey the importance of the time-sensitive nature of the drug product (to be taken as soon as possible within 72 hours of intercourse) it also misleadingly implies immediate or instantaneous action that does not take into account the time course for adverse sequelae. Some women may experience spotting a few days after taking the drug product, menstrual changes for the subsequent menses, or common side effects such as nausea, abdominal pain, fatigue, and headache. In addition, a follow-up physical or pelvic exam may be warranted if the general health or pregnancy status of the patient is in question. Therefore, these two proposed trade names may create a false sense of safety by creating the misleading impression that the drug product's effects, particularly those that are adverse, are immediate and complete. b(4)

Without substantial evidence to support such a time limited response implication, the proposed trade names are misleading.

Please note that 21 CFR 201.10(c)(3) provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

In response to DDMAC's 'Plan B _____' and '_____ ' comments, the Division of Reproductive and Urologic Products in an August 16, 2006 e-mail stated that they do not concur with DDMAC's comments. Specifically, the Division stated that, "the names [Plan B _____ and _____], do not minimize the (slight) risks associated with the product, and do properly convey the sense that the product should be taken as soon as possible after unprotected intercourse. Issues of adverse events, effects on menstrual cycle, etc. will be appropriately handled in labeling." However, the Division stated that they had some concern with the potential for confusion if 'Plan B' stays on the market as a prescription or an over-the-counter (OTC) product while concurrently marketing the name 'Plan B _____' for the proposed product. b(4)

It is DMETS' understanding that the Sponsor plans on marketing an OTC version of Plan B, while still marketing their currently approved prescription product, Plan B. The Division stated that the prescription version of Plan B will be indicated for women under 18 years of age while the OTC version will be available to women 18 years of age and older. Given this information, DMETS has the following concerns with the use of the proposed names, 'Plan B _____', 'Plan B _____', and _____ b(4)

A. Plan B _____ and Plan B _____ b(4)

DMETS is concerned about the potential for 'Plan B _____' or 'Plan B _____' to be confused with 'Plan B'. This can occur because Plan B will remain on the market. The modifiers _____ or '_____ ' may suggest that the currently marketed drug, Plan B, must be taken 'one time' or 'immediately' and may not convey to patients and healthcare providers that what is intended to be given is a different drug product with a higher strength (0.75 mg vs. 1.5 mg) and different dosing frequency (twice daily vs. once daily). Additionally, the recipient of a prescription for 'Plan B _____' or 'Plan B _____' may misinterpret it as administering one package of 'Plan B', or administering "Plan B" as soon as possible. Since the dosage strengths and frequency of administration varies between the already existing drug product (Plan B) and the proposed product (Plan B _____, Plan B _____), DMETS is concerned that the patient receiving the drug might receive a subtherapeutic amount, should they receive dosing instructions for the latter but receive the former product. In other words, if they receive Plan B by mistake, but were told to take it once, they would only ingest half of the appropriate dose. The ramifications of this error being that the woman may not have the desired effect. b(4)

Additionally, since both the 'Plan B' and 'Plan B _____, Plan B _____' products will be kept in the pharmacy, we wonder if incidents will arise in which the prescription version will mistakenly be placed adjacent to the non-prescription version, resulting in a selection error and delivery or administration of the wrong product. b(4)

B. _____

The name ' _____ may be confused with dosage instructions, such as "STAT", which indicate that the drug product must be taken immediately. Utilizing a name that is associated with a common administration term may produce confusion. Additionally, we have not allowed sponsors to use names that are "instructional". A pharmacist who receives a prescription for ' _____ - UD", may be led to believe that the prescriber omitted the drug name by mistake. DMETS is concerned that further clarifying this prescription with the prescriber may lead to a delay in administration, which is problematic since _____ is a time sensitive product and must be administered within a 72 hour window. Not receiving the drug during this time period may increase the likelihood of an unwanted pregnancy.

b(4)

b(4)

b(4)

C. Availability of Prescription and Over-the-Counter Product

The OTC version will be kept behind the pharmacy counter, however, DMETS questions how the packaging of either product will be differentiated and whether having both Rx and OTC versions with the same name will increase the likelihood for medication errors. We also wonder how the age restrictions will be enforced since anyone underage (less than 18 years) may easily ask their peers to attain the medication.

For the aforementioned reasons, DMETS does not recommend the use of the proposed proprietary names, 'Plan B _____, Plan B _____, and " _____'. If you have any questions for DDMAC, please contact Suzanne Berkman or Michelle Safarik at 301-796-1200. If you have any other questions or need clarification, please contact the Medication Errors Project Manager, Diane Smith, at 301-796-0538.

b(4)

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/s/

Jinhee Jahng
8/17/2006 05:10:17 PM
DRUG SAFETY OFFICE REVIEWER

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8/18/2006 09:42:56 AM
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8/18/2006 09:52:01 AM
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 25, 2006

TO: Dan Shames, M.D., Director
Division of Reproductive and Urologic Products

VIA: Nenita Cristostomo, R.N., Regulatory Health Project Manager
Division of Reproductive and Urologic Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS review of the Patient Labeling (Carton) for _____
Tablet (levonorgestrel), NDA 21-998

b(4)

Background and Summary

Duramed Research, Inc., a subsidiary of Barr Pharmaceuticals submitted an NDA for _____ mg (levonorgestrel), NDA 21-998, on January 24, 2006, for emergency contraception. _____ Tablet is the single dose version of the already approved and marketed Plan B® (2 x levonorgestrel 0.75 mg tablets), NDA 21-045 (approved July 28, 1999).

b(4)

Patient labeling (carton) was submitted for review. This labeling is identical to the Plan B patient labeling (carton) with the exception of the dosing instructions and adverse event incidence.

Comments and Recommendations

1. The patient labeling is acceptable from a patient comprehension perspective.
2. The statement, " _____ ; is not a helpful instruction unless the patient has refills on her prescription.

b(4)

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/s/

Jeanine Best
5/25/2006 03:34:33 PM
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5/26/2006 12:18:01 PM
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