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RESEARCH**

APPLICATION NUMBER:

21-998

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 9, 2009
From	Lisa M. Soule, M.D., Division of Reproductive and Urologic Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-998
Supplement#	Complete Response
Applicant	Duramed Pharmaceuticals, Inc.
Date of Submission	January 12, 2009 (received)
PDUFA Goal Date	July 12, 2009
Proprietary Name / Established (USAN) names	Levonorgestrel tablet Plan B One-Step
Dosage forms / Strength	Tablet, 1.5 mg
Proposed Indication(s)	To prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure
Recommended:	Approval

1. Introduction

Levonorgestrel (hereafter referred to as LNG) is a second generation gonane progestin commonly used in combined oral contraceptives. It is currently available for the indication of emergency contraception as Plan B[®] (NDA 21-045, initially approved in 1999), a product administered as two doses of 0.75 mg LNG each, taken 12 hours apart, starting as soon as possible within 72 hours after unprotected intercourse. Since August 2006, Plan B has been available in the US as an-over-the counter (OTC) product for women aged 18 and above, while remaining prescription-only (Rx) for women under 18.

In this application, the Applicant seeks to market a single dose regimen of the same product, i.e., a single 1.5 mg LNG tablet to be taken as soon as possible within 72 hours after unprotected intercourse. In addition, the Applicant seeks dual Rx/OTC marketing, but with the age for OTC access lowered by one year (i.e., to women age 17 and older) from that originally approved for Plan B.

The proposed regimen, LNG 1.5 mg single dose, is approved for marketing in more than 25 countries. Full OTC distribution of LNG for emergency contraception has been approved in Canada, Holland, Sweden, Norway and India, and is about to be made available OTC in Spain.

2. Background

Regulatory History of Plan B

Plan B, LNG 0.75 mg tablets (administered in two doses, 12 hours apart), was approved for the indication of emergency contraception in 1999, and a supplement to switch the product from prescription to OTC status was submitted on April 16, 2003 by the then-Applicant, Barr Research, Inc. Despite recommendations for approval of this application by this Division, the

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Office of Drug Evaluation III, the Division of Over-the-Counter Drug Products, the Office of Drug Evaluation V and the Office of New Drugs, as well as by the Non-Prescription Drugs and Reproductive Health Drugs Advisory Committees (voting 23:4 for a switch to OTC status without age restrictions), the Acting Director of the Center for Drug Evaluation and Research (CDER) issued a Not Approvable letter on May 6, 2004 stating that the supplement did not provide adequate data demonstrating the safety and efficacy of the product for OTC use by women under the age of 16.

The Applicant (by then known as Duramed Research, Inc.) submitted a Complete Response on July 21, 2004, proposing a change in product marketing to OTC status for women aged 16 and above, while maintaining prescription-only status for women under age 16. On August 26, 2005, the Commissioner of the FDA notified the Applicant that CDER had concluded that submitted data were sufficient to support use of Plan B as an OTC product only for women aged 17 and older. However, unresolved issues precluded a decision on the approvability of the submission:

- Whether an Rx/OTC split in marketing could be done based solely on the age of the user
- How an age-based distinction could be enforced
- Whether a single package could be used to market prescription and OTC versions of the same active ingredient

The Agency further requested public comment on whether rulemaking should be initiated to codify the Agency's interpretation of the statute regarding when a product may be simultaneously marketed as prescription and OTC.

Over 47,000 public comments were received and summarized, and on July 31, 2006, the Acting Commissioner notified the Applicant that the Agency had determined that rulemaking was not necessary and that further evaluation of the application was proceeding. Following a meeting with CDER on August 8, 2006, and submission of several amendments, the Applicant proposed revised labeling and a Convenient Access Responsible Education (CARE) program, restricting OTC sales to women aged 18 and above. A memorandum by the Acting FDA Commissioner, dated August 23, 2006, cited concerns about the enforceability of the age restriction with respect to women under the age of 18 and stated his decision that "In considering the difficulty of enforcing an age-based restriction on the availability of this oral hormonal contraceptive, I have concluded that 18 (rather than 17) is the more appropriate cutoff point to best promote and protect the public health." On August 24, 2006, the Applicant was issued an approval to market Plan B as a prescription product for women under age 18, and as an OTC product for women 18 and above.

Initial Application for a Single-Dose LNG Emergency Contraceptive

During the interval where action on the Plan B application was pending the Agency's receipt and review of public comments, a preNDA meeting was held between the Division and the Applicant on January 13, 2006, to discuss the Applicant's plan to submit an NDA for a single-dose version of Plan B, based upon a single randomized clinical trial conducted by the WHO. On January 24, 2006, the Applicant (officially Gedeon Richter, with Duramed Research, Inc. as authorized US agent) submitted NDA 21-998, proposing a single dose regimen of 1.5 mg LNG (hereinafter referred to as Plan B One-Step) as a prescription only product for the

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indication of emergency contraception. This proposal for prescription-only marketing mirrored the availability of Plan B at the time of the NDA submission.

However, with the approval of Plan B as a dual Rx/OTC product during the review cycle of Plan B One-Step, it was not possible to approve the marketing of the single dose drug as a prescription-only product when same active ingredient was available OTC for women age 18 and above. Therefore, on November 22, 2006, the Division issued an Approvable letter, stating

We have completed our review of this application, as amended, and it is approvable. As you are aware, levonorgestrel tablets consisting of two 0.75 mg doses taken 12 hours apart are approved, with the same total dosage, for prescription-only (Rx) use for emergency contraception in women 17 years of age and younger and for nonprescription (over-the-counter or OTC) use in women 18 years of age and older. Your application proposed marketing a 1.5 mg levonorgestrel tablet as a prescription-only product for women of all ages. FDA has evaluated the data incorporated by reference into your application concerning actual use and labeling comprehension in relation to levonorgestrel for emergency contraceptive use. These data establish that the 1.5 mg levonorgestrel product can safely and effectively be used as an OTC product for women ages 18 and over. Therefore, before this application may be approved, you will need to submit revised labeling that meets the requirements of marketing of levonorgestrel tablets, 1.5 mg, as a prescription product for women 17 years of age and younger, and as a nonprescription product for women 18 years of age and older. You will also need to submit your plan regarding distribution of both the Rx and OTC versions of your product.

Current application (Complete Response)

The Applicant (initially Gedeon Richter, ownership changed to Duramed Pharmaceuticals, Inc. on June 26, 2009) submitted a Complete Response on January 9, 2009, initially seeking approval to market the single dose product OTC to women age 18 and up, and by prescription only to women under age 18. At the time of the submission, a case was ongoing in the US District Federal Court in NY (*Tummino v. von Eschenbach et al*) that had been filed by the Center for Reproductive Rights concerning the FDA's decision process for the Plan B Rx/OTC application, and the decision to restrict OTC access to Plan B to women age 18 and above. On March 23, 2009, a final decision was reached in the case. The court ordered the FDA to act within 30 days to extend OTC access to women age 17 and above.

On April 21, 2009, the Director of the Division of Nonprescription Clinical Evaluation (DNCE) sent a letter to the Applicant explaining that scientific reexamination of the age limit for OTC access led DNCE to conclude that there was no evidence supporting a distinction between ages 17 and 18 with regard to enforcing the age restriction for OTC access. This letter outlined what would be required if Duramed decided to pursue OTC marketing of Plan B for women age 17 and older. On April 22, 2009, FDA issued a press release stating that "...FDA notified the manufacturer of Plan B informing the company that it may, upon submission and approval of an appropriate application, market Plan B without a prescription to women 17 years of age and older."

The Division received a meeting request from the Applicant on April 28, 2009 to discuss revision of the patient population eligible for OTC access to women age 17 and above, and of

prescription access only for women under age 17, for both Plan B and Plan B One-Step. On June 1, 2009, a meeting was held between the Division of Reproductive and Urologic Products (DRUP), the Office of Nonprescription Products (ONP), the Office of New Drugs (OND) and the Applicant. Other than revised labeling, no new requirements were imposed for approval of Plan B One-Step for dual OTC and prescription status for women 17 and above and under 17, respectively. Amended labeling (to address the lowering of the OTC age by one year) and a safety update were subsequently submitted by the Applicant on June 9, 2009.

3. CMC/Device

There were no outstanding CMC issues at the time of the Approvable action, aside from labeling, which had been deferred. This Complete Response was placed on a six-month clock due to the need for reinspection of the drug substance manufacturing site. The site was deemed ACCEPTABLE on February 10, 2009.

The primary Chemistry Reviewer, Donna Christner, Ph.D., made the following recommendations in her review dated June 16, 2009:

This NDA can be APPROVED from a CMC standpoint. The Office of Compliance has made an overall ACCEPTABLE recommendation for all manufacturing and testing sites. Labeling is adequate.

Expiry of 24 months was granted. No phase 4 commitments were requested.

4. Nonclinical Pharmacology/Toxicology

There were no outstanding Pharmacology/Toxicology issues at the time of the Approvable action, aside from labeling issues, which were deferred.

The primary Pharmacology/Toxicology reviewer, Lynnda Reid, Ph.D., made the following recommendations in her review dated April 22, 2009:

Recommendations on approvability: Pharmacology recommends approval of levonorgestrel 1.5 mg for use in women seeking emergency contraceptive for occasional use after a contraceptive accident or unprotected sex.

Recommendations for nonclinical studies: None

Recommendations on labeling: To comply with the Physician's Labeling Rule, the following labeling should replace

Carcinogenicity: There is no evidence of increased risk of cancer with short-term use of progestins. There was no increase in tumorigenicity following administration of levonorgestrel to rats for 2 years at approximately 5 µg/day, to dogs for 7 years at up to 0.125 mg/kg/day, or to rhesus monkeys for 10 years at up to 250 µg/kg/day. In another 7 year dog study, administration of levonorgestrel at 0.5 mg/kg/day did increase the number of mammary adenomas in treated dogs compared to controls. There were no malignancies.

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Genotoxicity: *Levonorgestrel was not found to be mutagenic or genotoxic in the Ames Assay, in vitro mammalian culture assays utilizing mouse lymphoma cells and Chinese hamster ovary cells, and in an in vivo micronucleus assay in mice.*

Fertility: *There are no irreversible effects on fertility following cessation of exposures to levonorgestrel or progestins in general.*

Dr. Reid's labeling recommendations were conveyed to the Applicant and agreement was reached on July 9, 2009.

5. Clinical Pharmacology/Biopharmaceutics

There were no outstanding Clinical Pharmacology issues at the time of the Approvable action, aside from labeling issues, which were deferred.

The Clinical Pharmacology reviewer, Hyunjin Kim, Pharm.D., M.S., made the following recommendations in his review dated June 22, 2009:

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 21-998 acceptable provided that agreement is reached between the sponsor and the Division regarding the language in the package insert.

Dr. Kim's labeling comments were conveyed to the Applicant, and agreement was reached on July 9, 2009. No phase 4 commitments were recommended.

6. Clinical Microbiology

A Microbiology consult was not needed for this application, as it is an oral tablet.

7. Clinical/Statistical - Efficacy

The primary reviewer, Daniel Davis, M.D., recommended in his review dated July 9, 2009:

I recommend that single dose 1.5 mg levonorgestrel, herein called Plan B One-Step, be approved as a prescription (Rx) drug, as requested by the Applicant, for emergency contraception for use up to 72 hours after known or suspected contraceptive failure or unprotected intercourse in women under age 17. Assuming approval by the Office of Nonprescription Products, the same product will be available over the counter (OTC) for women age 17 and older.

Team Leader Comment

I concur with Dr. Davis' recommendation.

A full discussion of efficacy data is contained in the initial clinical reviews, the Medical Officer review and the Team Leader review, both dated November 22, 2006. Only a brief summary is presented here.

The Applicant submitted data from a large randomized, double-blind, multicenter World Health Organization (WHO) trial (Study 97902). This trial randomized 4,136 women who presented within 120 hours after unprotected intercourse to one of three arms – mifepristone 10 mg, LNG 0.75 mg, administered in two doses 12 hours apart, or LNG 1.5 mg in a single

dose. As the Applicant was only requesting an indication for use within 72 hours after unprotected intercourse, data on the subset of women who presented for treatment within the first 72 hours formed the primary basis of evaluation.

Supportive efficacy information was submitted based upon a literature publication of a Nigerian study¹ comparing the safety and efficacy of the two dose regimen of LNG 0.75 mg with a single dose of 1.5 mg LNG. In this study, 1,160 women presenting within 72 hours of unprotected intercourse were randomized into one of the two regimens.

Both the WHO and the Nigerian studies evaluated the observed numbers of pregnancies under each dosing regimen of LNG as compared to the expected number of pregnancies. In both studies, the expected numbers of pregnancies were estimated by multiplying the number of women having unprotected intercourse on each day of the menstrual cycle (relative to the estimated day of ovulation) by the probability of conception on each cycle day. Results were expressed in terms of pregnancy rate in each arm, prevented fraction of pregnancies (calculated as 1 - [expected number of pregnancies/observed number of pregnancies]), and as the relative risk of pregnancy in the single dose regimen as compared to the two-dose regimen.

The primary efficacy variables in the WHO trial were the pregnancy rate with its 95% confidence interval and the prevented fraction with its 95% confidence interval. Efficacy was evaluated in the full intent to treat (ITT), defined as all randomized subjects with any assessment of efficacy available.

The primary efficacy analysis (see Table 1) showed similar prevented fractions for the single dose and two-dose LNG regimens (84% and 79%, respectively). The overlapping confidence intervals for the two regimens indicate that the differences in prevented fraction were not statistically significant.

Table 1 Efficacy Results in WHO Trial (Full ITT Population, enrolled within 72 hours of unprotected intercourse)

Group	N	Observed Pregnancies				Expected Pregnancies	Prevented Fraction		
		#	Rate	95% LL	95% UL	#	PF*	95% LL	95% UL
LNG Single Dose	1198	16	1.3356	0.7653	2.1598	99.7	83.95	73.94	90.83
LNG Two-Dose	1183	20	1.6906	1.0357	2.5990	94.9	78.92	67.44	87.12

* PF: prevented fraction of pregnancies

Source: Adapted from Table 2, Applicant's submission of November 8, 2006, p 3

Team Leader Comment

Efficacy, as measured by the prevented fraction of expected pregnancies, is acceptable for both dose regimens; there is no evidence of a lessening of effectiveness with utilization of a single dose regimen.

Data from the supportive Nigerian study are shown in Table 2.

¹ Arowojolu AO et al. Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians. Contraception 66: 269-73, 2002

Table 2 Efficacy in Nigerian Study

Group	N	Observed Pregnancies				Expected Pregnancies	Prevented Fraction		
		#	Rate	95%LL	95%UL	#	PF*	95%LL	95%UL
LNG one dose	573	4	0.69	0.02	1.38	57.1	92.99	81.25	97.38
LNG two dose	545	7	1.28	0.34	2.20	53.1	86.80	72.07	93.77

* PF: prevented fraction of pregnancies

Source: Primary Medical Review, dated November 22, 2006, Table 12, p 25

Team Leader Comment

The prevented fraction in both arms of the Nigerian study was equivalent to, or slightly better than that demonstrated in the WHO study.

Statistical review

The original submission was reviewed by Sonia Castillo, Ph.D., who stated the following in the "Conclusions" of her review dated September 26, 2006:

From a statistical standpoint, the Sponsor has provided an adequate study that resulted in a prevented fraction of 81.9% (95% C.I. from 72.0% to 88.9%) for levonorgestrel 1.5 mg tablet for use as an emergency contraceptive to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

As Dr. Castillo's original conclusion was based on efficacy data for treatment within 120 hours of unprotected intercourse, an Addendum to the Statistical review was filed on November 21, 2006, stating that Dr. Castillo reviewed and verified the Applicant's analyses of the subgroup of women presenting for treatment within 72 hours of unprotected intercourse.

Dr. Castillo reviewed the labeling proposed in the Complete Response and made the following conclusion in her review dated June 16, 2009:

...this portion of the clinical studies section of the label in this Class 2 labeling resubmission is acceptable from a statistical perspective.

Overall assessment of efficacy

The overall assessment of efficacy is reproduced here from the November 2006 Team Leader review:

Both the large, pivotal WHO trial and the supportive study conducted in Nigeria provide acceptable evidence of the effectiveness of a single dose regimen of 1.5 mg of LNG as an emergency contraceptive when taken within 72 hours of unprotected intercourse. In both trials, the prevented fraction of expected pregnancies, calculated based upon the probability of pregnancy for the cycle day on which each woman had intercourse, was above 80% (similar to that seen in the original Plan B two-dose trial) for the single dose regimen. In both trials, the prevented fraction was numerically greater in the single dose than the two-dose arm, although this was reported to be statistically significant only in the Nigerian trial. Similarly, the relative risk of pregnancy in the single dose regimen as compared to the two-dose regimen was not statistically significantly different from 1.0, indicating that the single dose regimen is at least as effective in preventing pregnancy as the two dose regimen.

Stratification of analysis by age in the WHO trial indicates that the single dose regimen is similarly efficacious in women above and below the age of 35. The apparent improvement in efficacy in older women is likely attributable to their reduced fecundity, rather than due to LNG effects.

Additional analyses highlight some potential limitations of the efficacy of LNG as an emergency contraceptive, which are currently documented in the Plan B label. The efficacy appears slightly lower in Chinese women than non-Chinese women, for reasons that are not completely clear. The difference between Chinese and non-Chinese women was not as great in this trial as in the original Plan B trial, and was not as marked in the single dose arm as in the two-dose arm; nonetheless, this should remain in the labeling for the proposed product.

The WHO trial demonstrated, and the Nigerian study reported, a deleterious effect on efficacy of delaying treatment, particularly beyond 72 hours of unprotected intercourse. While the effects are not linear when analyzed by day of presentation, it is clear that women in the WHO trial who did not initiate treatment until 97-120 hours after unprotected intercourse had a much lower prevented fraction of pregnancies. Repeat acts of unprotected intercourse subsequent to treatment were also associated with lower efficacy in both trials. The Current Plan B label describes the importance of taking LNG emergency contraception within 72 hours of unprotected intercourse; this should also be labeled in the proposed product. The adverse impact of subsequent unprotected intercourse on treatment efficacy should also be labeled.

8. Safety

A full discussion of safety is contained in the initial clinical reviews, the Medical Officer review and the Team Leader review, both dated November 22, 2006. Only a brief summary is presented here, along with a summary of the safety update submitted with the Complete Response.

First cycle submission

In the initial submission, there were no deaths in either study, and only three serious adverse events (SAEs) were reported in the WHO trial (a ruptured corpus luteum cyst, acute appendicitis and an ectopic pregnancy in a subject treated with two-dose LNG); the Nigerian study did not report any adverse events (AEs) as serious. Subjects were queried about common anticipated adverse events in the WHO trial, and the following frequencies were reported:

Table 3 Adverse Events in WHO Study

Adverse event	Single dose Levonorgestrel N = 1,379		Two dose Levonorgestrel N = 1,377	
	# of Reports	*Rate (%)	# of Reports	Rate (%)
Bleeding	426	31	426	31
Nausea	189	14	199	14
Lower abdominal pain	183	13	198	14
Fatigue	184	13	182	13
Headache	142	10	130	9
Dizziness	132	10	126	9
Breast tenderness	113	8	115	8
Delay of menses > 7 days	61	4.5	61	4.5
Diarrhea	53	4	44	3
Vomiting	19	1.4	19	1.4

Source: Primary Medical Review, dated November 22, 2006, Table 15, p 30

The Nigerian data, based on spontaneous reports, were similar, with commonly reported AEs (8-23% of subjects) consisting of nausea and vomiting, dizziness, headache, breast tenderness, lower abdominal pain and menorrhagia.

The impact of LNG treatment, whether by single dose or two-dose regimen, on the menstrual cycle was fairly minimal in the WHO study, whether measured in terms of delay of menses or increased severity of bleeding. More than half of all subjects experienced menses within two days of the expected time. In each group, 4.5% of women experienced a delay of seven or more days beyond the expected date of menses. Women were asked to characterize their period following treatment as "less, similar, more or much more" than their normal menses. Twelve percent of each group experienced bleeding that was "more" (11% each) or "much more" (1% each) than normal menses. In the Nigerian trial, 20% of the single dose group had a delay in the onset of menses of seven or more days after expected, compared to 15% in the two dose group. The rate of "heavy menses" was also greater in the single dose group, as noted above.

A safety update was submitted by the Applicant, providing the periodic safety update report for the period January 1, 2006 to June 30, 2006 prepared by Gedeon Richter Ltd, which markets both 0.75 and 1.5 mg LNG products for emergency contraception. Gedeon Richter estimated that over the reporting period, more than [redacted] uses of LNG emergency contraception occurred; more than [redacted] in the 60 countries in which the two-dose regimen was marketed and [redacted] in the 21 countries in which the single dose regimen was sold. A total of 105 adverse event reports were received; there were no withdrawals or suspensions of marketing authorization for safety reasons. Among the adverse events reported were 20 cases of pregnancy occurring after use of emergency contraception, and one case of pruritis. The remaining reports were of non-serious, listed, unconfirmed, or follow-up adverse events.

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In September 2006, the FDA's Office of Surveillance and Epidemiology (OSE) reviewed all the adverse event reports naming Plan B or levonorgestrel for emergency contraception found in the FDA's adverse event reporting system (AERS) database. When reviewed by age groups, OSE concluded that the data in AERS do not indicate that adverse events in adolescents (age 14-19) are different from those seen in older age groups.

The overall assessment of safety as described in the 2006 Team Leader review was:

The safety profile for a single dose regimen of 1.5 mg LNG is similar to that seen with the approved two-dose regimen, which has been found to be safe enough to qualify for OTC availability, at least for women aged 18 and above. There were no serious adverse events likely to be attributable to the drug in the single dose regimen of the pivotal clinical trial. A single ectopic pregnancy occurred in the two-dose arm of the WHO trial, which may be drug-related; however, the occurrence of a single ectopic among 44 pregnancies (based upon the entire safety population presenting within 120 hours of unprotected intercourse) is within the expected range of 1-2%. The Gedeon Richter postmarketing safety data based upon more than _____ uses of LNG emergency contraception and AERS reports, upon a background of _____ JS uses of Plan B, do not suggest any significant safety concerns.

b(4)

Safety update to current submission

The Applicant provided a safety update consisting of recent safety reports covering the US marketed two-dose product (Plan B) along with European data on both single dose and two-dose products. In addition, the Office of Safety and Evaluation (OSE) Division of Pharmacovigilance II (DPV II) updated a review of AERS reports for Plan B through May 14, 2009. Dr. Davis' primary medical review provides details on the reports describing the US and global data.

Duramed submitted a 12-month Periodic Adverse Drug Event Report (PADER) for Plan B covering July 2007 – June 2008, which included 9,029 individual reports, of which only seven were listed as serious and medically confirmed. Of the ten most commonly reported AEs, eight are already described in labeling, and the Applicant plans to add dysmenorrhea and pelvic pain to the Plan B label in the Postmarketing section. The Applicant also plans to monitor as part of ongoing pharmacovigilance the following adverse events (AEs) of interest in the PADER: hypersensitivity (four reports), loss of consciousness (seven reports), syncope (six reports), dyspnea (27 reports) and erythema nodosum (one report). Duramed plans to develop a data collection form to obtain more comprehensive medical information about any future cases of loss of consciousness/syncope.

The global report was prepared by Gedeon Richter, the manufacturer of Plan B and Plan B One-Step, and also the distributor of identical products in a number of foreign countries. This Periodic Safety Update Report (PSUR) covered the last half of 2008, and reported 219 new cases, on a background of about _____ uses of two-dose or single dose LNG products. The three most commonly reported AEs were spontaneous abortion, irregular bleeding, and delayed menstruation. Gedeon Richter plans to update the Company Core Data Sheet with the AEs of dysmenorrhea and pelvic pain.

b(4)

Team Leader Comments

- Two of the three most commonly reported AEs are currently discussed in labeling – irregular bleeding and delayed menstruation.
- Given that LNG does not prevent 100% of pregnancies following unprotected intercourse, and given the known rate of spontaneous abortions (about 25% of all conceptions), the reports of spontaneous abortion are not unexpected and do not constitute a safety signal.

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The DPV II review evaluated all domestic AE reports in women under age 18 from the 1999 market approval to the present, and also all domestic AE reports in women of all ages from March 12, 2008 (the time of the last major OSE safety review) through May 14, 2009. Only 13 reports concerned women under age 18, while 73 reports were received concerning women of all ages from the more limited timeframe. Dr. Davis' primary review contains details of the case reports. The overall profile of AEs was similar for younger women. The serious unlabeled AEs reported included uterine hemorrhage, hematemesis, loss of consciousness, dysmenorrhea and syncope. These five AEs also had data mining scores indicative of a possible safety signal (see Comment below).

Team Leader Comments

- **In-depth review of the hemorrhage and hematemesis cases did not find evidence of a safety signal, however.**
- **In 2008, OSE noted the possible safety signal for syncope and loss of consciousness, stating the "suggestion of a possible temporal relationship with Plan B administration..." The Division agreed that OSE should continue pharmacovigilance for these AEs. The Applicant now plans to monitor closely for these AEs as part of ongoing pharmacovigilance.**
- **The Applicant has proposed adding dysmenorrhea and pelvic pain to the Postmarketing section of labeling for Plan B. The Division has requested that this information also be included in the Plan B One-Step label.**

No new fatalities have been reported in the most recent review, and only two fatalities have ever been reported in association with the use of Plan B – one in a 21 year old woman with extensive concomitant drug use, which was determined by OSE to be unlikely to be associated with Plan B, and one a neonatal death of a severely premature infant.

In summary, OSE "did not identify any new safety signals for Plan B that warrant labeling changes" and plans to continue pharmacovigilance of Plan B.

Overall assessment of safety

The safety profile for the single dose product, based on clinical trial data and postmarketing data from other countries that market a single dose product, does not differ from that of the approved two-dose Plan B. Based on the recent AERS review, there is no evidence of an altered safety profile among women under the age of 18 who use LNG emergency contraception, whether obtained by prescription or OTC. I find no evidence to suggest that there is any safety-based rationale to justify restricting OTC access, particularly for the age group requested by the Applicant, women age 17 and above.

In the absence of US postmarketing data on the single dose product, I believe the label should include postmarketing safety data based on the two-dose product. This is an important addition to the clinical trial safety data. The clinical trial data are based on anticipated adverse events about which subjects were specifically queried, and with the exposure of a broader population once the product is marketed, it is to be expected that a fuller safety profile will emerge.

As noted by both the Applicant and OSE, there may be an emerging safety signal of syncope and loss of consciousness. I do not believe the postmarketing reports rise to the level of labeling at this time, but I concur with the plan by both groups to continue active surveillance of these adverse events. I see no indication that these events occur differentially among users categorized on the basis of age.

9. Advisory Committee Meeting

The original Plan B Rx to OTC switch application was the subject of a 2003 meeting of the Advisory Committees for Reproductive Health Drugs and Nonprescription Drugs. The joint Committee recommended by a vote of 23 to 4 that Plan B was sufficiently safe to be distributed over-the-counter without any age or distribution restrictions and without any further studies before approval.

The Division determined that an Advisory Committee was not needed to review the current application, as it did not raise new safety or efficacy concerns.

10. Pediatrics

The Applicant requested a partial waiver and partial extrapolation for pediatric studies. The Division recommended a partial waiver for premenarcheal patients, who are not at risk of pregnancy, and that the pediatric study requirement was met by extrapolation of adult data to postmenarcheal adolescents. The request was reviewed by the Pediatric Review Committee (PeRC) on April 8, 2009; PeRC agreed to grant a full waiver of the pediatric study requirement.

11. Other Relevant Regulatory Issues

None

12. Labeling

The Applicant's originally proposed name "Plan B _____" was not acceptable to the Division of Medication Error Prevention and Analysis (DMEPA), and was withdrawn by the Applicant. The alternative name "Plan B One-Step" was found acceptable by DMEPA in their review dated May 1, 2009, and the Division concurred in this decision.

b(4)

Several issues were noted in the first cycle review that warranted inclusion in prescription labeling and were addressed in labeling in the current application:

- Higher pregnancy rate in Chinese women
- Decreased efficacy with delay in treatment beyond 72 hours of unprotected intercourse

In reviewing the proposed labeling submitted in the amended Complete Response submission, the following items were negotiated with the Applicant, with resolution reached that was satisfactory to both the Division and the Applicant:

- Characterization of the age cutoff between Rx and OTC access ("younger than age 17 years" and "17 years and older," respectively)
- Instructions in case of vomiting within two hours after taking the tablet (the labeling directed toward healthcare providers says "consideration should be given to repeating the dose," while that for patients says "immediately contact your healthcare provider to discuss whether to take another tablet.")
- Inclusion of postmarketing data based on Plan B in the Postmarketing subsection of the Adverse Reactions section

In addition, since the first cycle, the Physicians Labeling Rule (PLR) has become the standard labeling format. The Applicant submitted labeling in PLR format, which represents a major

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change in format, although only minor change in content, as compared to the current label for the approved Plan B product. New sections that now exist in PLR labeling, but were not previously included in the Plan B label, include:

- Highlights
- Dosage Forms & Strengths
- Warnings & Precautions (formerly two separate sections)
- A Postmarketing subsection within Adverse Reactions
- Nonclinical Toxicology section (with a subsection for Carcinogenesis, Mutagenesis, Impairment of Fertility)
- Patient Counseling Information

Other alterations related to the conversion to PLR format include:

- Removal of _____ b(4)
- Removal of _____
- Movement of the statement that Plan B is not for routine use as a contraceptive from _____ to Indications and Usage section
- Reordering of sections within Warnings & Precautions to reflect level of seriousness
- Revision and updating of the Drug Interactions section _____
- Removal of the _____ b(4)

Labeling was also reviewed by the Division of Drug Marketing, Advertising, and Communications (DDMAC) and by DMEPA. Their comments were conveyed to the Applicant as appropriate, and addressed in the agreed-upon labeling.

The Consumer Information Leaflet (CIL) was reviewed by the Office of Nonprescription Products and agreement was reached with the Applicant. There is no formal patient package insert for the prescription product because all consumers receive the CIL.

Carton and container labeling was reviewed by DMEPA and by the CMC reviewer; and their comments were addressed by the Applicant. Carton and container labeling was also reviewed by the Office of Nonprescription Products.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action: Approval**

From the perspective of safety and efficacy, I believe that levonorgestrel 1.5 mg should be approved for marketing. In the initial application in 2006, the Applicant requested approval to market levonorgestrel 1.5 mg as a prescription-only product for all ages. This was not permissible, given that there was a very similar product (Plan B) available OTC to women aged 18 and up.

In the current submission, the Applicant requests dual Rx/OTC marketing, with the drug available by prescription only to women under age 17. While I continue to believe that Plan B One-Step as used by women of any age does not meet the criteria specified in

21CFR§330.10(a)(4)(vi) to determine that a drug “may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs,” the Applicant is not currently seeking full OTC status for Plan B One-Step. Therefore, in the interests of making available an emergency contraceptive product that likely offers a compliance benefit over the currently approved product, I recommend that an approval action be taken on levonorgestrel 1.5 mg for the dual marketing as proposed by the Applicant.

- **Risk Benefit Assessment:**

In light of the low level of risk inherent in this single dose, single use emergency contraception regimen, coupled with its high efficacy (>80%) in preventing pregnancy ensuing from unprotected intercourse, which in itself may pose significant medical, psychological and social risks, there is a favorable risk/benefit ratio for the single dose LNG 1.5 mg product. The simplicity of the proposed new regimen using a single, one tablet dose, leads me to conclude that the product could be safely used by women of all ages in the absence of a “learned intermediary;” i.e., the product is appropriate for OTC marketing to all women of childbearing age. However, the Applicant has requested dual Rx/OTC marketing, with OTC availability restricted to woman age 17 and above.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies: None**

No significant safety signals have been identified with use of the currently marketed prescription/OTC product, Plan B, in the foreign postmarketing data pertaining to the single dose product, or in the clinical trials for the proposed single dose regimen. I believe LNG 1.5 mg is safe for use by women of all ages, and that risk management steps are not needed.

- **Recommendation for other Postmarketing Requirements and Commitments: None**

The approval of Plan B as a dual Rx/OTC product included a postmarketing agreement to conduct a program entitled CARE to provide information to consumers, to educate providers and consumers, to ensure distribution of Plan B through appropriate distributors and to monitor compliance with labeling, particularly with regard to the restriction of OTC availability only to women age 18 years or older. The Applicant has conducted this evaluation since the 2006 approval, and has reported the findings to FDA, as agreed. The results have demonstrated excellent levels of compliance with the dual marketing age restrictions. I concur with Dr. Davis that the programs have successfully focused on and accomplished the four core elements of the company’s objectives.

The Applicant submitted a marketing, education, distribution and monitoring program also called CARE, to be extended to Plan B One-Step. This program is very similar to the original Plan B CARE, and provides for annual reporting of findings to FDA.

The current submission seeks only to lower the age for OTC access by one year. As noted in Dr. Leonard-Segal’s April 2009 letter to the Applicant, there do not appear to be any compliance issues suggesting that pharmacists are unable to distinguish the patient subgroup that needs a prescription from those women who are eligible for OTC access. I do not see any necessity to require a CARE program for Plan B One-Step; however, I find it acceptable as a voluntary effort by the Applicant.

Cross Discipline Team Leader Review
NDA 21-998 Plan B One-Step Complete Response
July 9, 2009

- **Recommended Comments to Applicant: None**

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this page is the manifestation of the electronic signature.**

/s/

Lisa Soule
7/9/2009 12:59:41 PM
MEDICAL OFFICER

Scott Monroe
7/9/2009 05:12:46 PM
MEDICAL OFFICER

I concur with Dr. Soule's conclusions and her recommendation
that Plan B One-Step (levonorgestrel) tablet, 1.5 mg,
be approved for marketing.