CLINICAL REVIEW

Application Type	Complete response to November 22, 2006 action letter
Application Number(s)	21-998
Priority or Standard	Standard
Submit Date(s)	January 9, 2009
Received Date(s)	January 12, 2009
PDUFA Goal Date	July 12, 2009
Division / Office	DRUP/ODE III
Reviewer Name(s)	Daniel Davis, MD, MPH
Review Completion Date	July 9, 2009
Established Name	Levonorgestrel 1.5 mg tablet
(Proposed) Trade Name	Plan B One-Step
Therapeutic Class	Emergency contraception
Applicant	Duramed Pharmaceutical, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	One tablet as soon as possible
Indication(s)	Emergency contraception
Intended Population(s)	Women of reproductive age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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.

It is important to note that the original recommendation (2004) from DRUP (Division of Reproductive and Urologic Products) and the Office of Drug Evaluation III (ODE III) regarding a switch from prescription to OTC status for the two-dose levonorgestrel emergency contraceptive product, Plan B, was that full OTC availability was acceptable, and that there did not need to be any age restriction. Furthermore, the joint Advisory Committees for Reproductive Health Drugs and Nonprescription Drugs met on December 16, 2003 to consider the Rx/OTC switch application for Plan B, and 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. I continue to believe, based on all the clinical trial results, available medical literature, and postmarketing data, that both Plan B and Plan B One-Step 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. Therefore, approving Plan B One-Step as an OTC product for women age 17 and above is consistent with the distribution plan that has been recommended by DRUP, ODE 3, and a joint Advisory Committee for levonorgestrel emergency contraception ever since the initial request for an Rx/OTC switch for Plan B.

The efficacy and safety for single dose 1.5 mg levonorgestrel appear to be the same as for the approved two dose levonorgestrel 0.75 mg (Plan B). For maximum effectiveness, either product should be taken as soon as possible after unprotected intercourse. Compliance for the single dose regimen should be much better than for the two dose regimen for Plan B because 1) only one dose is required, and 2) the Plan B 12-hour dosing requires potential night-time dosing (e.g., 3 pm and 3 am).

1.2 Risk Benefit Assessment

The safety of levonorgestrel in lower daily doses in oral contraceptive pills taken for routine contraception and in the higher (1.5 mg total) dose for emergency contraception has been well-established. The total dose of 1.5 mg levonorgestrel is the same for both Plan B and Plan B One-Step. There are no signals in the current NDA or from extensive worldwide postmarketing reports of single dose levonorgestrel 1.5 mg product that suggest the single dose regimen will have a different safety profile from the two dose regimen approved in 1999 in the US.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The approval of Plan B as a dual Rx/OTC product included a postmarketing agreement to conduct a plan entitled the CARE^{SM} Program which included a Point-of Purchase Monitoring Program to monitor compliance with labeling, particularly with regard to the restriction of OTC availability only to women age 18 or older. The Applicant has conducted this program since the 2006 approval, and has monitored findings of the program and reported to FDA, as agreed. The results have demonstrated excellent levels of compliance with the dual marketing age restrictions. It is my opinion that the CARE and Point-of Purchase Monitoring Programs have successfully focused on and accomplished the four core elements of the company's objectives with the programs.

As far as marketing restrictions, the current submission seeks only to lower the age for OTC access by one year, as compared to the age restriction currently in force for Plan B. As noted in a letter sent by Dr. Leonard-Segal of the Division of Nonprescription Clinical Evaluation (DNCE) letter to the Applicant in April 2009, there do not appear to be any compliance issues suggesting that pharmacists are unable to distinguish the patient populations who need a prescription from those who are eligible for OTC access. Although the Applicant voluntarily submitted a CARE and Point of Purchase Monitoring program for Plan B One-Step on January 9, 2009 and June 30, 2009, with minor revisions on July 9th, I do not see any necessity to formalize it as a postmarketing requirement or commitment.

2 Introduction and Regulatory Background

In July 1999, levonorgestrel 1.5 mg (divided into two 0.75 mg tablets taken 12 hours apart), was approved for emergency contraception in the U.S. under NDA 21-045 and has been used extensively since then, marketed as Plan B. The Applicant submitted Supplement 011 to NDA 21-045 on April 22, 2003 for a switch from prescription status to OTC status for Plan B. In December 2003, a joint Advisory Committee (Reproductive Health Drugs and Nonprescription Drugs) meeting was held to discuss the switch from prescription status to OTC status. The 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 original PDUFA date was February 22, 2004 and a 3-month extension was granted, extending the date to May 22, 2004.

On May 6, 2004 the Applicant received a Not Approvable letter from the Agency. The primary reason for the action was that the CDER Acting Center Director believed that "you have not provided adequate data to support a conclusion that Plan B can be used safely by young adolescent women for emergency contraception without the

professional supervision of a practitioner licensed by law to administer the drug." The Applicant, called Barr Laboratories at the time, was informed that before the application could be approved, they would need to either provide additional data demonstrating that Plan B can be used safely by women under age 16 without professional supervision or supply information in support of marketing Plan B as a prescription-only product for women under the age of 16 years and a nonprescription product for women age 16 years and older.

On July 21, 2004, the Applicant submitted a Complete Response to the Not-Approvable letter and requested that Plan B remain available by prescription only for women under age 16 and be switched to OTC status for women age 16 and older. On August 26, 2005, the Commissioner of the FDA, Dr. Lester Crawford, 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

On August 24, 2006, the Agency made the final decision that Plan B be approved for OTC status for women age 18 and older and remain as prescription-only for women under age 18. Although the action letter signed by Dr. Steven Galson, Director of CDER, does not explicitly state it, there were concerns expressed in an August 23, 2006 memo by FDA Commissioner Dr. Andrew von Eschenbach about the ability of pharmacies (and thus their professional staff) to enforce the age restriction with respect to purchases by women under age 17 without a prescription. Dr. von Eschenbach believed that the existing infrastructure utilized to restrict certain products (e.g., tobacco) to consumers aged 18 and above could be used to enforce the limitation of OTC access to Plan B to women age 18 and above.

NDA 21-998 for the single dose levonorgestrel product was originally submitted on January, 24 2006. An “approvable” action letter was sent to the Applicant on November 22, 2006. The letter stated the following:

> “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.
>
> Further comments on labeling are deferred until the above deficiency is addressed.
>
> When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level."

On January 9, 2009, the Applicant submitted their Complete Response to the action letter dated November 22, 2006. The Applicant initially requested approval of the single dose product for prescription use for women age 17 and younger and for OTC availability for women age 18 and older.

Subsequently, on March 23, 2009, a final decision was reached in the US District Federal Court (NY) case *Tummino v. von Eschenbach et al.* concerning the FDA's decision process and restriction to age 18 and older for the OTC switch for Plan B. The plaintiffs' claim was that the FDA's decisions "were arbitrary and capricious because they were not the result of reasoned and good faith agency decision-making." The court ordered the FDA to act within 30 days to extend the OTC access to 17 year-olds. On April 22, 2009, a press release by the FDA stated 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." At the same time, the Director of DNCE sent a letter to Duramed outlining what would be required if Duramed decided to pursue OTC marketing of Plan B for women age 17 and older.

The Division received a meeting request from Duramed on April 28, 2009 to discuss inclusion of the patient population age 17 and older for OTC marketing and under age 17 for prescription availability, for both Plan B and Plan B One-Step. On June 1, 2009, a meeting was held between DRUP (Division of Reproductive and Urologic Products), ONP (Office of Nonprescription Products), OND (Office of New Drugs) and the Applicant. Other than the requirements outlined in the November 2006 action letter, there were no new major requirements for approval of Plan B One-Step for dual OTC and prescription status. Amended labeling (to address the lowering of the OTC age by one year) and a safety update were required and were subsequently submitted by Duramed on June 9, 2009.

2.1 Product Information

See previous NDA reviews for NDA 21-045 (Plan B) and 21-998 (Plan B One-Step).

2.4 Important Safety Issues with Consideration to Related Drugs

Levonorgestrel is a progestin hormone. For products containing a progestin only, as opposed to a combination progestin and estrogen, and used as a single use treatment for emergency contraception, there are no issues of concern. There is a well-established favorable safety (risk/benefit) profile for progestin-only drugs used for routine hormonal contraception and especially when limited to a single use for emergency contraception.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

See detailed discussion in Section 2 above.

Labeling:
The label originally proposed for One-Step in the 2006 submission was in the standard format. In the Complete Response, the Applicant submitted the label in the new Physician's Labeling Rule (PLR) format; this was subsequently edited by the various disciplines at the Agency and draft edits were sent to the Applicant on May 13, 2009. Further comments and edits from the Applicant were submitted back to the Divisions (DRUP and DNCE) on June 9, 2009. Final agreement on the labeling was reached on July 9, 2009.

Safety Update:
On June 9, 2009, the Applicant submitted two documents for their safety update. This included summary pages from the July 2007 to July 2008 Periodic Adverse Drug Event Report (PADER) for Plan B and the Gideon Richter PSUR (periodic safety update report) covering the period from July 2008 through December 2008 with data for both the two-dose and single-dose products.

2.6 Other Relevant Background Information

Refer to section 2.0 for relevant background information.

3 Ethics and Good Clinical Practices

See the original NDA reviews. No issues were noted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There are none.

5 Sources of Clinical Data

The primary source of clinical data is the randomized, double-blind WHO Study 97902 with over 2,700 women using levonorgestrel, either two-dose or single-dose, for

emergency contraception. Supportive data is from the randomized, double-blind Nigerian study with over 1,100 women using levonorgestrel for emergency contraception, for which only the publication (not the source data) was submitted. Both of these trials were blinded and directly compared the single dose and two dose regimens using a total dose of 1.5 mg levonorgestrel.

WHO Study 92908, the pivotal trial for the approval of Plan B in 1999, was a prospective blinded trial that directly compared the two-dose levonorgestrel regimen with the Yuzpe regimen (levonorgestrel + ethinyl estradiol). Data from this trial was not reviewed again, but was also considered supportive of the safety and efficacy of levonorgestrel for emergency contraception because the total dose of levonorgestrel was exactly the same.

6 Review of Efficacy

Efficacy Summary

The two levonorgestrel regimens (single dose and two-dose) are highly effective for emergency contraception. The World Health organization (WHO) 97902 study showed that in the full intent to treat (ITT) population of women who used emergency contraception within 72 hours of intercourse, the single dose 1.5 mg levonorgestrel regimen had a slightly better, but not statistically significantly different, effectiveness (84% of expected pregnancies prevented) compared to the two dose 0.75 mg levonorgestrel (79% of pregnancies prevented). See Table 1, reproduced from the original NDA review.

Table 1 Summary Pregnancy Rates and Prevented Fractions (0-72 hour subset)

Patient Population	Pregnancy Rate (Percent)		Pregnancy Prevented Fraction (Percent)	
	Group 1 (single dose)	Group 2 (2 dose)	Group 1 (single dose)	Group 2 (2 dose)
Full ITT	1.34	1.69	84.0	78.9
Restricted ITT	1.22	1.52	85.3	81.3
Per Protocol	1.23	1.54	85.1	80.9

Source: Adapted from Applicant's Tables 2-4 submitted 11-08-06 (Response to Division IR).

A trend towards a lower efficacy with a longer delay in taking single dose levonorgestrel 1.5 mg after unprotected intercourse was evident when considering the pregnancy rates for two time intervals (initiation of treatment between 0 to 72 hours versus 73 to 120 hours) after unprotected intercourse.

Concerning efficacy it is important to emphasize the following:

1. Take the treatment for emergency contraception as soon as possible after unprotected intercourse, and within 72 hours of the event.

2. Further acts of intercourse before the onset of the next menstrual period should be discouraged, as this will increase the chances of an unplanned pregnancy.
3. Treatment is effective for women of all reproductive ages.
4. Effectiveness in Chinese women may be slightly, but not statistically significantly, lower compared to non-Chinese women.
5. Treatment does not protect against HIV and other sexually transmitted infections.
6. Lastly, treatment is for emergency contraception and not for routine contraception.

Since the November 2006 review of the data in the NDA, there are no further substantial data from clinical trials or the medical literature that bear upon the efficacy of the single dose 1.5 mg levonorgestrel product.

6.1 Indication

Plan B One-Step is indicated for emergency contraception for use up to 72 hours after known or suspected contraceptive failure or unprotected intercourse in women of all reproductive ages.

7 Review of Safety

7.1 Methods

Safety Summary (original NDA review)

For the original NDA 21-998 review, the safety profile for single dose 1.5 mg levonorgestrel was based on data from two blinded, randomized clinical trials, plus global postmarketing experience in 27 countries, and is essentially the same as that observed for the two-dose 0.75 mg levonorgestrel product (Plan B). The most common adverse events in the data submitted from the adequate and well-controlled clinical trials are the following in descending frequency: vaginal bleeding, nausea, lower abdominal pain, fatigue, headache, dizziness, breast tenderness, delay of menses > 7 days, and diarrhea. These are listed in the proposed label and are not serious. The risk /benefit ratio for single dose levonorgestrel is acceptable. The prevention of an unplanned pregnancy and its inherent risks far outweigh the adverse events associated with taking a single dose of 1.5 mg levonorgestrel.

Safety Review (new materials and consults)

The following new information was reviewed for this safety update:

1. AERS update by DAEA (Division of Adverse Event Analysis)[1] for Plan B through 3-08

[1] Due to restructuring of the Office of Surveillance and Epidemiology (OSE), formerly called the Office of Drug Safety, the DAEA division was renamed DPV II. The AERS updates looked at the same database and essentially used the same analytic tools.

2. AERS update by DPV II (Division of Pharmacovigilance II, formerly named DAEA) for Plan B through 5-09
3. PSUR (periodic safety update report) from the European manufacturer Gideon Richter for July through December 2008 with over (b) (4) uses of their levonorgestrel products (submitted 6-9-09)
4. PADER from the Applicant for Plan B covering July 2007 to July 2008 (submitted 6-9-09)
5. OTC and pharmacy availability, provided by the Applicant
6. Scientific literature since the original review

AERS Updates:

All adverse event reports submitted to the FDA either directly from the manufacturer or from individuals are collected in the AERS (adverse event reporting system) database. This database was reviewed twice by the experts in the Office of Surveillance and Epidemiology (OSE) to look for any new signals or safety concerns. The two updates were completed in April 2008 and June 2009. The Executive Summary from the 2008 review follows:

> "A comprehensive review of Plan B® (levonorgestrel tablets 0.75 mg) was undertaken upon receipt of the sponsor's U.S. Periodic Report and approximately a year has elapsed since the dually labeled product for Rx or OTC use was released to pharmacies. This comprehensive review included a review of potentially significant data mining scores for Plan B and searches in the AERS database for the most commonly reported preferred terms and reports of congenital anomalies, fatalities, and thromboembolic events for Plan B. This comprehensive review of Plan B data mining scores and reports in the AERS database did not identify any adverse events that should be considered for inclusion in the labeling at this time. For the reports of syncope and loss of consciousness reviewed herein, there was a suggestion of a possible temporal relationship with Plan B administration in this small case series. The division should consider requesting that the sponsor conduct a comprehensive review of syncope and loss of consciousness.
>
> The sponsor stated in the U.S. Periodic Report for the period of 01 July 2006 through 30 June 2007 that they will conduct an assessment of all reports of pelvic pain and dysmenorrhea, which were primarily non-serious reports. The DAEA (Division of Adverse Event Analysis) will continue to monitor this product for any new potential safety signals or events of concern (i.e. thromboembolic events)."

The 29-page review looked at the most commonly reported preferred terms, fatal outcomes (one adult case), congenital anomalies and pregnancy complications, and thromboembolic events. DRUP did not concur that the sponsor (Duramed) needed at the time to conduct a comprehensive review of syncope and loss of consciousness, but agreed that DAEA should continue to monitor the AERS reports and the Applicant

should do the same. Based on this AERS update, DRUP did not recommend any labeling changes or new postmarketing studies.

The Executive Summary from the recent DPV 2009 review follows:

> "This safety review is an update of a comprehensive review of Plan B completed by the Division of Pharmacovigilance II (DPV [formerly DAEA]) 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 domestic cases [age range 15-17] 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."

The second review also did not ascertain any new safety signals. Only 13 US reports were found for younger women (age 17 or less) since the approval of Plan B in 1999. These were:

- Tylenol overdose
- Nosebleed, menstrual-like cramping
- Vaginal bleeding
- Abdominal pain and vomiting
- Dizziness and fainting (fainting after watching her boyfriend "feed a mouse to a snake")
- Dizziness, non-menstrual stomach pain, hematemesis
- Miscarriage
- Abdominal pain, fainting
- Vomiting, shortness of breath
- Loss of consciousness, 5 seconds
- Positive pregnancy test (2 reports)
- Neonatal death of premature infant (age 3 days)

This reviewer agrees with the conclusion that none of these 13 reports raised new safety issues in this younger patient population. Four of the reports involve dizziness/fainting, which will continue to be monitored by the Applicant and our Office of Surveillance and Epidemiology (by the DPV II).

There are limited reliable data on use of Plan B in women age 17 and under, but data through June 6, 2009 from (b) (4) and (b) (4) (submitted by the Applicant) shows that on average, approximately (b) (4) written prescriptions are filled weekly in the US. This equates to (b) (4) written prescriptions annually.

PSUR (periodic safety update report) update:

Gedeon Richter:

Gedeon Richter has manufactured levonorgestrel 1.5 and 0.75 mg tablets for decades; it is the supplier for Plan B and Plan B One-Step, as well as being the distributor for the two products in several countries worldwide under a variety of tradenames. The twentieth PSUR for levonorgestrel from Gedeon Richter is the most recent report. It covers the 6-month period from 7-01-08 to 12-31-08 and includes individual case safety reports (ICSRs) and other data collected by Gedeon Richter. There were (b) (4) and (b) (4) uses for the two-dose and single dose products, respectively. Overall, 230 individual cases with a total of 528 adverse reactions were received related to levonorgestrel during the 6-month reference period; 219 were new cases and 11 were follow-up reports. During this period there were no clinical trials conducted by the manufacturer. Content modifications in the Reference Safety Information based on the PSUR data include the following:

1. Headache will be changed from the common to very common adverse event column
2. Two new adverse events will be added to the update section of the Company Core Data Sheet (CCDS): dysmenorrhea and pelvic pain. Both belong to the same MedDRA System Organ Class- Reproductive system and breast disorders and were reported with the same frequency: very rare (< 1/10,000).
3. Text was added that (b) (4)

During the reporting period, the three most commonly reported adverse events were spontaneous abortion, irregular bleeding, and delayed menstruation. These three events are expected with emergency contraception. Spontaneous abortion (miscarriage) occurs because emergency contraception does not prevent all pregnancies and the natural spontaneous miscarriage rate is at least 10% of all pregnancies. Irregular bleeding and delayed menstruation are common because it is well established that emergency contraception may act by disrupting or delaying ovulation and subsequently altering the current menstrual cycle.

There was no new marketing authorization, withdrawal, revocation, or suspension of the Gedeon Richter levonorgestrel products. There were no restrictions on distribution, dosage modification, formulation changes, or urgent safety restrictions.

Analyzing the overall report of the 219 new cases, 47 were considered by the reporting source to be serious, unlisted, and confirmed. These 47 case reports came from regulatory authorities, contractual partners, and healthcare providers. This included 11 reports of congenital anomalies, 15 reports of missed or spontaneous abortions, leaving only 21 cases in all other categories. There were two reported cases of thrombocytopenic purpura, and one case each for pancreatitis, overdose, CVA, convulsion, and VTE. Given the exposure of over (b) (4) uses, this number of cases is not alarming and there is no evidence that they are directly related to the use of levonorgestrel for emergency contraception.

In summary, this reviewer does not see any new safety signals in the data reported by Gedeon Richter in their 20th PSUR covering well over (b) (4) uses of levonorgestrel for emergency contraception. The Applicant has proposed adding dysmenorrhea and pelvic pain to the Adverse Reaction section of the Plan B label, and the Division has requested that similar information be added to the postmarketing section in the Plan B One-Step label as well. Although I disagree that women under 16 years of age should not take levonorgestrel without medical supervision, this point is moot at this time as the Applicant (Duramed) is seeking prescription approval for women under age 17, so medical supervision would be *de facto* provided to women under age 17.

Duramed (Plan B):

The Applicant submitted the 55-page Narrative Summary and Analysis from the latest PADER for Plan B, the two-dose levonorgestrel 0.75 mg product. The summary covers the 12 months from 7-01-07 to 6-30-08. This periodic report contains 9,029 Individual Case Safety Reports. 8,981 of these reports were non-serious, while 48 were serious; however 99.7 % of the 9,029 cases were from non-healthcare providers and not confirmed. Seven case reports from five individuals were medically confirmed and serious with two events considered expected and five events unexpected. Upon further investigation, the two “expected” events were ectopic pregnancies, and the five “unexpected” were spontaneous abortion, missed abortion, blood in urine, pancreatitis, and cytomegalovirus (CMV) infection. Spontaneous abortion and missed abortion in my opinion are expected because some pregnancies are expected and of these there is at least a 10% chance of a spontaneous or missed abortion (i.e., a “miscarriage”). However, the regulatory definition of an “unexpected” adverse event relates to the lack of inclusion of that event in labeling, rather than to the likelihood of such an event occurring in association with use of the product. The blood in urine was reported with one of the ectopic cases where vaginal bleeding can commonly contaminate a urine sample. The pancreatitis was diagnosed five days after taking Plan B and was secondary to CMV infection; Plan B was not considered in the report to be related to the events. These seven medically confirmed events in five subjects do not raise any new concerns and, in my opinion are not serious and unexpected, with the exception of the case with pancreatitis due to CMV infection.

During the 12-month review period, approximately (b) (4) units were sold either OTC or by prescription. Because of advanced provision of Plan B, a relatively common practice in the US, a patient dispensed Plan B may not have used it, so precise data on actual usage is not known. Of interest is that there was a 384% increase in the reporting rate for adverse events in the 8-month period following the switch from prescription (Rx) only status to the dual-label OTC/Rx status in November 2006. The total units of Plan B sold during this same time period increased by (b) (4). The reports come from various US sources, including healthcare providers and consumers, and from any global reports that were considered both serious and unexpected.

There were no serious, unexpected reports from the scientific literature. The first table below, copied from page 3 of 55 of the PADER, shows the source of the 9,029 reports, which contained a total of 15,432 adverse events. The second table lists the ten most frequently reported adverse events for Plan B during the period 7-01-07 to 6-30-08.

Table 3.1.A. Distribution of Plan B® Postmarketing Adverse Events by Source, Seriousness and Expectedness during the period July 1, 2007 to June 30, 2008

	Total AEs	Serious		Non-Serious	
Healthcare Professionals	47	Expected	Unexpected	Expected	Unexpected
		2	5	28	12
Non-Healthcare Professionals	15,385	16	46	11,735	3,588
Total	15,432	18	51	11,763	3,600

Table 3.1.B. Most Frequently Reported Adverse Events by Preferred Term during the Period from July 1, 2007, to June 30, 2008

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	
Dysmenorrhoea	653
Menstruation irregular	5505
Oligomenorrhoea	533
Pelvic pain	733
Total	**11,497**

From the table above, the five most frequently reported adverse events were menstruation irregular (5,505), nausea (1,275), pelvic pain (733), dysmenorrhea (653), and abdominal pain (632). These events were predominantly non-serious and currently labeled except for pelvic pain and dysmenorrhea. This reviewer believes that pelvic pain and dysmenorrhea should be incorporated in the Plan B One-Step label until the time that there is sufficient postmarketing data specifically with the use of Plan B One-Step. High dose levonorgestrel for emergency contraception intentionally disrupts the ovarian (hormonal) cycle, so it is not surprising that the most common events are related to reproductive hormonal changes and menstrual cycle symptoms.

The analysis provided by the Applicant in the summary systematically analyzes the reports for each event of medical significance, grouped by SOC. Cases included in more than one section of the summary are cross-referenced. All MedDRA preferred terms (PTs) for the case are also listed. The analysis is thorough and detailed and each

case is identified with the manufacturing control number so further scrutiny is easily possible. The Applicant's brief conclusion in the Summary is the following:

> "Hypersensitivity, Loss of consciousness, Syncope, Dyspnea and Erythema nodosum will be closely monitored as part of ongoing pharmacovigilance for Plan B. Pregnancy experience will continue to be monitored as part of ongoing pharmacovigilance for Plan B. As a follow-up to last year's analysis, a comprehensive safety assessment of all reports of pelvic pain and dysmenorrhoea was performed and can be found in Appendix 1. Based on a review of this assessment, a labeling change will be considered as deemed necessary.
>
> Based on available safety information from this reporting period, the current US prescribing information adequately describes the benefit-risk profile for Plan B."

There were four medically unconfirmed response of hypersensitivity during the 12-month reporting period. Two of the cases were reported to have occurred the same day as Plan B was taken; one case had symptoms consistent with a mild anaphylactic reaction, but none of the cases noted a hospitalization. There were seven medically unconfirmed reports of loss of consciousness and six unconfirmed reports of syncope occurring in eleven women. The lack of details in the reports made a thorough safety assessment difficult. Confounding factors such as alcohol intake, pregnancy, and concomitant medications were noted in some of the cases. According to the PADER report, the reporting rate of these events has remained steady from the previous year. For future cases, a collection form will be developed in an attempt to obtain more comprehensive medical information for cases involving these events.

A total of 27 non-medically confirmed cases noting dyspnea were received. One case was considered to be serious. Eighteen of the women experienced dyspnea within 24 hours of taking Plan B and 12 had persistent symptoms at the time of the report. None of the women were hospitalized. Compared to the previous year reporting period, the reporting rate of cases with dyspnea has been stable. It seems reasonable to this reviewer that the Applicant to continue to monitor this symptom as planned.

The one case of erythema nodosum is the first time this event has been reported for Plan B. It is expected for oral contraceptives, but not for Plan B. Although it does not seem especially warranted because of its rare occurrence, the Applicant will monitor erythema nodosum as part of their ongoing pharmacovigilance for Plan B.

In summary, this reviewer does not see any new significant safety signals in the data reported by Duramed in their PADER covering well over (b) (4) uses of levonorgestrel for emergency contraception over a recent 12-month time span. The Applicant will continue to closely monitor hypersensitivity, loss of consciousness, syncope, dyspnea, and erythema nodosum. Pregnancy outcomes (spontaneous abortions, term deliveries, and ectopics) do not raise any concerns. Furthermore, there are no specific labeling changes that I would recommend for the Plan B One-Step label with one exception based on the report: heavier menstrual bleeding, lower abdominal pain, and nausea are already listed as three of the most common adverse events reported in clinical trials. Although dysmenorrhea and pelvic pain were not commonly

reported in the large comparative clinical trial for Plan B One-Step, I believe that the postmarketing data found in the Plan B label, including dysmenorrhea and pelvic pain, should be included in the Plan B One-Step label until the time that there is sufficient postmarketing data specifically with the use of Plan B One-Step.

Global Pharmacy and OTC availability:

By March 2009, levonorgestrel for emergency contraception was available without a prescription from a pharmacist in 44 countries and nine states in the US with approved pharmacy access programs. It was available OTC without any age restriction in five countries: Canada (June 2009), Norway, Sweden, Holland, and India; and in the US for ages 18 and older. In China, official policy is that emergency contraception pills (ECPs) are to be obtained from a pharmacist, but in practice the majority of women are able to purchase ECPs directly off the shelf without consulting a pharmacist. In May 2009, Spain announced that emergency contraception would be available over the counter in pharmacies without prescription within three months.

The extensive pharmacy and OTC availability globally, including the US, is reassuring that levonorgestrel for emergency contraception is safe and can be appropriately selected by women of all ages.

Scientific Literature since November 2006:

Several articles in the scientific literature from 2006 to the present were reviewed. They covered the following topics:

1. Advance provision of emergency contraception: Cochrane review
2. Levonorgestrel for emergency contraception: safety, efficacy, availability, comparative clinical trial data
3. Effect of emergency contraception use on pregnancy risk behavior
4. Improving contraceptive use and reducing unintended pregnancies in the US
5. Population effect of increased access to emergency contraception: a systematic review
6. Comparative safety, effectiveness, and access of interventions for emergency contraception: 2008 Cochrane review
7. American Society for Emergency Contraception semi-annual updates
8. Reports from several organizations in the US and globally on research, safety and efficacy, and distribution for emergency contraception products

From the scientific literature over the past three years there have been no new safety concerns associated with the use of levonorgestrel for emergency contraception. Despite the marked increase in pharmacy and OTC availability, there is substantial evidence that women do not use the product as often as they ideally should to prevent unintended pregnancies. This, however, is a compliance or behavioral issue and not a

safety issue. The overwhelming evidence from the literature is that levonorgestrel is safe, efficacious, and well-tolerated.

Overall Safety Conclusion:

Based on the review of safety data covering ten years of Plan B use in the US since 1999, safety data in the original NDA 21-998, the new materials/data discussed above, and a review of recent scientific literature, my overall safety conclusion is that levonorgestrel 1.5 mg, whether taken as a single dose, or two doses 12 hours apart, is safe and well-tolerated and has a favorable benefit/risk profile. Furthermore, there is no safety issue or evidence from the scientific literature or OTC availability globally that would preclude lowering the OTC population age from 18 to 17 years of age or even lower.

It should be noted that, as expected, the C_{max} for the single dose 1.5 mg levonorgestrel product is higher than found with the two-dose 0.75 mg Plan B product (based on administration of a single tablet). There is no evidence that this is a safety or efficacy concern. The single dose levonorgestrel 1.5 mg product is approved in several countries worldwide and no precautions or warnings relative to the higher C_{max} are found in the labels for these products. There do not appear to be any safety signals in the NDA review or from extensive postmarketing data that show a safety (adverse event profile) difference between the two products.

Furthermore, it is important to note that the original recommendation from DRUP and the Office of Drug Evaluation III for the OTC availability of Plan B was that there did not need to be any age restriction. The joint Advisory Committee that met on December 16, 2003 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. I continue to believe, based on all the clinical trial results, available medical literature, and postmarketing data, that both Plan B and Plan B One-Step could be safely used by women of all ages in the absence of a “learned intermediary;” i.e., the levonorgestrel emergency contraception is appropriate for OTC marketing to all women of childbearing age regardless of their age.

7.2 Adequacy of Safety Assessments

Safety data and assessments have been adequate. Safety assessments have analyzed data from many randomized clinical trials, OTC availability in at least 6 countries (including the US since late 2006), adverse event reporting in the US through the MedWatch system and AERS database, and postmarketing experience in over 80 countries globally. There has been an extensive use of levonorgestrel 1.5 mg (as a two-dose and single dose product) in millions of women in the US and an even larger number of women globally.

7.4 Supportive Safety Results

This comes from the widespread use of levonorgestrel-containing contraceptive products (oral, implants, and intrauterine devices) that have been on the US market

since 1982 (27 years). In addition to its use as an emergency contraceptive tablet, levonorgestrel is found in combination hormonal contraceptive products (containing a progestin and an estrogen) and levonorgestrel-alone products.

7.6 Additional Safety Evaluations

A thorough safety update (36 pages plus 38 references) written by this reviewer in March 2004 found no significant signals of concern for human carcinogenicity, human reproduction and pregnancy data, pediatrics and assessment of effects on growth, overdose, drug abuse potential, or withdrawal and rebound effects.

7.7 Additional Submissions / Safety Issues

There are none.

8 Postmarket Experience

In the US the single dose levonorgestrel product has not been marketed, although it is common knowledge that the two-dose Plan B is often administered off-label, with both tablets being taken at a single time. It is impossible to tell from the AERS database whether individuals who report an adverse event used a 12-hour dosing or a single dosing. There is, however, substantial use of approved single dose levonorgestrel products for emergency contraception globally. The data from Gedeon Richter alone shows at least (b) (4) single dose uses in a recent six month period; Gedeon Richter products for emergency contraception are approved in at least 25 different countries. Globally there are over 20 manufacturers of levonorgestrel products for emergency contraception that are approved in over 80 countries.

9 Appendices

9.1 Literature Review/References

See discussion under Review of Safety, Section 7.1.

9.2 Labeling Recommendations

After several labeling exchanges/negotiations with the Applicant, agreement was reached on July 9, 2009 for the final label for the prescription product. I recommend that the prescription label for Plan B One-Step (levonorgestrel) tablet, 1.5 mg, for oral use for women under the age of 17 be accepted as edited.

Labeling Consultations within the Agency included the following:

1. DMEPA (Division of Medication Error Prevention and Analysis) tradename review
2. DDMAC (Division of Drug Marketing, Advertising, and Communications) review
3. OTC label review

4. Input from all disciplines involved in the original NDA review: pre-clinical pharmacology, clinical pharmacology, chemistry, biometrics, and clinical
5. An update by DPV II for levonorgestrel use in the US for emergency contraception to determine if there are any safety signals that should be included in the Plan B One-Step label

DRUP agrees with the conclusions stated in the Executive Summary from the DMEPA review concerning the product tradename:

> "This review was written in response to receipt of an April 21, 2009 request for review of the proprietary name Plan B One-Step. This submission was made at the request of the FDA following discussion with the applicant on April 20, 2009 when we objected to the use of the proposed proprietary name Plan B (b) (4) for the reasons outlined in the discussion of this document. The proposed proprietary name Plan B One-Step is acceptable to the FDA for the proposed product. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation."

The review from DDMAC was received on June 23, 2009. Comments were made concerning several statements in the Prescribing Information (PI) for healthcare providers and the Patient Product Information (PPI) for consumers. DDMAC recommended that statements making promotional and unsubstantiated safety claims be deleted or modified. The Division made such changes as appropriate to the label in the version that was sent to the Applicant on June 26, 2009.

Because Plan B One-Step will be marketed as both a prescription and OTC product, the basic labels for the product must be the same. DRUP and DNCE are in agreement concerning the final label for the prescription and OTC product. The consult from DPV II did not find any new safety signals that should be specifically noted in the Plan B One-Step label other than the information already found in the current approved Plan B (two-dose) label.

The label revision also includes comments from all of the disciplines involved in the original NDA review.

Labeling Issues for the prescription product that needed extra discussion were the following:

1. The exact wording to express the age limitations for the prescription and OTC labels; the Division preferred that the label state that Plan B One-Step is "available over the counter for women 17 and older, and by prescription only for women under 17." In the **Highlights of Prescribing Information** and the **Full Prescribing Information** sections of the final label under **Indications and Usage** it states: "Plan B One-Step is available only by prescription for women younger than age 17 years, and available over the counter for women 17 years and older."

2. In the **Full Prescribing Information** portion of the final label under **2 Dosage and Administration**, the Division and Applicant agreed, and the label states: "If vomiting occurs within two hours of taking the tablet, consideration should be given to repeating the dose." In the **17.1 Information for Patients** section, women are advised: "If you vomit within two hours of taking the tablet, immediately contact your healthcare provider to discuss whether to take another tablet."

3. The Applicant wanted to (b) (4) The Applicant acknowledges that levonorgestrel 1.5 mg is marketed worldwide by Gedeon Richter, Schering, and several other companies, but proposed that (b) (4) DRUP believes that some postmarketing data for levonorgestrel emergency contraception should be included in the postmarketing section of the prescription label rather than (b) (4) . Final agreement was reached with the Applicant and section **6.2 Postmarketing Experience** reads as follows:

   > The following adverse reactions have been identified during post-approval use of Plan B (2 doses of 0.75 mg levonorgestrel taken 12 hours apart). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
   >
   > *Gastrointestinal Disorders*
   > Abdominal Pain, Nausea, Vomiting
   >
   > *General Disorders and Administration Site Conditions*
   > Fatigue
   >
   > *Nervous System Disorders*
   > Dizziness, Headache
   >
   > *Reproductive System and Breast Disorders*
   > Dysmenorrhea, Irregular Menstruation, Oligomenorrhea, Pelvic Pain

4. In section **8 Use in Specific Populations**, the Applicant wanted (b) (4) In the NDA trial a slightly higher pregnancy rate was seen in Chinese women (1.50%) versus non-Chinese women (1.44%), but it was not statistically significant. The same finding was found in the original Plan B NDA data and it is so labeled. (b) (4) Although the reason for the finding is unknown, DRUP and this reviewer believe that such information is helpful to both the prescriber and the consumer and should be included in the

final prescription label. The Sponsor agreed to the following text in the final prescription label:

> No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in Chinese women with both Plan B and the Yuzpe regimen (another form of emergency contraception). There was a non-statistically significant increased rate of pregnancy among Chinese women in the Plan B One-Step trial. The reason for this apparent increase in the pregnancy rate with emergency contraceptives in Chinese women is unknown.

9.3 Advisory Committee Meeting

In December 2003, an Advisory Committee was held to discuss the switch from prescription status to OTC status for two-dose Plan B (NDA 21-045). As noted earlier in this review, the 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. At this time there is no indication for a second Advisory Committee meeting for the same issue since the two products are practically the same. Plan B has been marketed as an OTC product for women age 18 and older in the United States since the approval in August 2006.

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/s/

Daniel Davis
7/9/2009 02:52:37 PM
MEDICAL OFFICER

Lisa Soule
7/9/2009 03:08:30 PM
MEDICAL OFFICER
I concur with Dr. Davis' conclusions and recommendation.