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RESEARCH**

*APPLICATION NUMBER:*

**21-998**

**SUMMARY REVIEW**

## Division Director Summary Review for Regulatory Action

<b>Date</b>	July 10, 2009
<b>From</b>	Scott Monroe, MD Division of Reproductive and Urologic Products
<b>Subject</b>	Division Director Summary Review
<b>NDA</b>	NDA 21-998 (Complete Response)
<b>Applicant Name</b>	Duramed Pharmaceuticals, Inc
<b>Date of Submission</b>	January 9, 2009
<b>PDUFA Goal Date</b>	July 12, 2009
<b>Proprietary Name / Established (USAN) Name</b>	Plan B One-Step Levonorgestrel
<b>Dosage Forms / Strength</b>	Oral tablet, 1.5 mg
<b>Proposed Indications (Prescription [Rx] and OTC)</b>	<b>Rx:</b> Emergency contraception for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure <b>OTC:</b> Reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)
<b>Action</b>	<i>Approve (see Section 13.1)</i>

<b>Material Reviewed/Consulted OND Action Package, including:</b>	<b>Names of Reviewers for Complete Response</b>
<b>Medical Officer Review</b>	Daniel Davis, MD
<b>Statistical Review</b>	Sonia Castillo, PhD/Mahboob Sobhan, PhD
<b>Pharmacology Toxicology Review</b>	Lynnda Reid, PhD
<b>CMC Review/ONDQA</b>	Donna Christner, PhD/Moo-Jhong Rhee, PhD
<b>Microbiology Review</b>	Not required
<b>Clinical Pharmacology Review</b>	Hyunjin Kim, PharmD/Myong-Jin Kim, PharmD
<b>DDMAC</b>	Janice Maniwang, PharmD, MBA
<b>DSI</b>	Not required
<b>CDTL Review</b>	Lisa Soule, MD (also Clinical Team Leader)
<b>OSE/DMEPA</b>	LaToya Tooms, PharmD/Carlos Mena-Grillasca, RPh
<b>OSE/DPV</b>	Mark Miller, PharmD/Melissa Truffa, RPh/Robert Boucher, MD/Gerald Dal Pan, MD
<b>DNCE</b>	Andrea Leonard-Segal, MD, Director of DNCE

OND	Office of New Drugs
DDMAC	Division of Drug Marketing, Advertising, and Communication
DSI	Division of Scientific Investigations
CDTL	Cross-Discipline Team Leader
OSE	Office of Surveillance and Epidemiology
DMEPA	Division of Medication Errors Prevention and Analysis
DPV	Division of Pharmacovigilance
DNCE	Division of Nonprescription Clinical Evaluation

## 1. INTRODUCTION

The objective of this new drug application (NDA 21-998) is to obtain marketing approval for Plan B One-Step (levonorgestrel tablet, 1.5 mg) for emergency contraception (i.e., for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure). The proposed dosing regimen is one tablet containing 1.5 mg of levonorgestrel to be taken as soon as possible within 72 hours after unprotected intercourse. Levonorgestrel (hereafter referred to as LNG) is a second generation gonane progestin commonly used in combination oral contraceptives.

Plan B (a product very similar to Plan B One-Step, but with a different dosing regimen) was approved for marketing for emergency contraception as a prescription-only product in 1999. The dosing regimen for Plan B is to take one tablet, which contains 0.75 mg LNG, as soon as possible within 72 hours after unprotected intercourse and a second tablet 12 hours after the first dose. Since August, 2006, Plan B has been available without prescription (i.e., over-the-counter [OTC]) for women 18 years of age and older and by prescription-only (Rx) for women younger than age 18 years.

NDA 21-998 was originally submitted for review in January, 2006. In the original NDA, the Applicant requested that Plan B One-Step (hereafter also referred to as LNG 1.5 mg) be available by prescription-only for all ages. However, with the approval of Plan B as a dual Rx/OTC product during the original review cycle for LNG 1.5 mg, it was determined that it was not possible to approve for marketing LNG 1.5 mg as a prescription-only product for emergency contraception for all ages because the same active ingredient (LNG) and same total dosage was available as a nonprescription product for the same indication for women 18 years of age and older. Therefore, on November 22, 2006, the Division of Reproductive and Urologic Products (DRUP) issued an Approvable letter that stated:

*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.*

During the original review cycle neither the primary Medical Reviewer nor the Clinical Team Leader identified any safety or efficacy issues, per se, that would have precluded approval of LNG 1.5 mg with appropriate labeling. Similarly, there were no unresolved chemistry,

manufacturing and control (CMC), clinical pharmacology, or nonclinical toxicology issues from the original review cycle. On January 9, 2009, the Applicant submitted a Complete Response, which included revised labeling in accordance with the Approvable letter. The Applicant did not submit any new CMC, clinical pharmacology, or nonclinical toxicology data.

## **2. BACKGROUND**

### **2.1 Regulatory History of Levonorgestrel Tablets for Emergency Contraception**

Plan B (LNG 0.75 mg tablets) was initially approved for emergency contraception under NDA 21-045 as a prescription-only product in July, 1999. The dosing regimen for Plan B is to take one tablet as soon as possible within 72 hours after unprotected intercourse and a second tablet 12 hours after the first dose. The Applicant subsequently submitted a Supplement to NDA 21-045 (Supplement 011) in April, 2003, to switch Plan B from prescription-only status to complete nonprescription (OTC) status. In December, 2003, a joint Advisory Committee Meeting (Reproductive Health Drugs and Nonprescription Drugs) was held to discuss the proposed switch to OTC status. The joint Committee recommended by a vote of 23 to 4 that Plan B be switched from prescription-only availability to OTC availability.

On May 6, 2004, the acting Director of the Center for Drug Evaluation and Research (CDER) issued a Not Approvable letter stating that the Supplement did not provide adequate data demonstrating the safety of the product for OTC use by young adolescent women. The Applicant was informed that before the Supplement could be approved, they would need to provide either (1) additional data demonstrating that Plan B could be used safely by women under age 16 without professional supervision or (2) information in support of marketing Plan B as a prescription-only product for women under the age of 16 years and as 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, then Commissioner of the FDA, 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 years and older. The Commissioner also stated that unresolved issues precluded a decision on the approvability of the Supplement. These issues included:

- 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. On July 31, 2006, then acting FDA Commissioner, Andrew von Eschenbach, notified the Applicant that the Agency had determined that rulemaking was not necessary and that further evaluation of the Application was proceeding. In a memo dated August 23, 2006, the acting Commissioner concluded that 18 years (rather than 17) was the more appropriate cutoff point because of general increased familiarity with 18 as a cutoff age, because 18 is the age of majority and retail outlets were familiar with using 18 as the

age restriction for the sale of certain products such as tobacco, nicotine replacement therapies, and pseudoephedrine products. On August 24, 2006, the Agency approved Plan B for marketing as an OTC product for women age 18 years and older and as a prescription-only product for women younger than age 18. The Approval letter also made reference to the Applicant's agreeing to conduct post-approval the educational and monitoring activities that were described in the Applicant's Convenient Access, Responsible Education (CARE) Program.

NDA 21-998 for LNG 1.5 mg was originally submitted for review in January, 2006. In the original NDA, the Applicant had requested that LNG 1.5 mg be available by prescription-only for all ages. However, with the approval of Plan B as a dual Rx/OTC product during the review cycle of LNG 1.5 mg, it was determined that it was not possible to approve for marketing LNG 1.5 mg as a prescription-only product for emergency contraception. Therefore, on November 22, 2006, DRUP issued an Approvable letter, as described earlier in the Introduction Section of this Review.

The Applicant submitted a Complete Response on January 9, 2009, seeking approval to market LNG 1.5 mg (1) OTC to women 18 years and older and (2) by prescription-only to women younger than age 18. At the time of the submission, a case was ongoing in the U.S. District Court for the Eastern District of New York (*Tummino v. von Eschenbach et al*) 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, the Court issued an order directing the FDA to permit, within 30 days, the Sponsor to make Plan B available to women ages 17 years and older without a prescription. In addition, the Court ordered FDA to reconsider whether to approve Plan B OTC without age or point-of-sale restriction.

On April 21, 2009, the Director of the Division of Nonprescription Clinical Evaluation (DNCE) sent a letter to the Sponsor explaining that 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. The letter also outlined what would be required if the Applicant decided to pursue OTC marketing of Plan B for women age 17 and older. In a subsequent meeting with the Sponsor, DNCE also stated that no additional information or justification, other than revised product labeling, would be needed to seek approval for LNG 1.5 mg (Plan B One-Step) for marketing as an OTC product for women age 17 and older and as a prescription-only product for females younger than 17 years.

## **2.2 Content of Complete Response**

The original Complete Response submission in January, 2009, included only (1) information regarding the proposed CARE (Convenient Access, Responsible Education) Program which is virtually identical to the on-going CARE Program for Plan B, (2) product labeling to support OTC availability for women age 18 years and older and prescription-only availability for females younger than age 18 years, and (3) updated stability information supportive of a 2 year expiry for LNG 1.5 mg tablets. Revised product labeling to support nonprescription availability for women 17 years and older and a safety update were submitted on June 9, 2009.

### **2.3 Recommendations of Primary Medical Reviewer and Clinical Team Leader regarding Approvability**

The primary Medical Reviewer, Dr. Daniel Davis, stated the following in his review, signed on 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 ..."*

*"... 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."*

Dr. Lisa Soule, the Cross-Discipline Team Leader (who was also the Clinical Team Leader), stated the following in her review, signed on July 9, 2009:

*"From the perspective of safety and efficacy, I believe that levonorgestrel 1.5 mg should be approved for marketing..."*

*"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."*

#### **Division Director's Comments**

- I concur with the recommendations of both Dr. Davis and Dr. Soule that LNG 1.5 mg be approved for emergency contraception. Although both believe that LNG 1.5 mg could be approved for OTC availability without any age restrictions, they both also support the Applicant's request that LNG 1.5 mg be approved for OTC availability for women 17 years and older and prescription-only availability for women under 17 years of age.*
- LNG 1.5 mg is approved for marketing in more than 25 countries. Full OTC availability of levonorgestrel (one and/or two dose regimens) for emergency contraception has been approved in Canada, Holland, Sweden, Norway and India, and it is about to be made available OTC without restriction in Spain.*

### 3. CMC

There were no outstanding CMC issues at the time of the Approvable action, aside from potential labeling issues, which were deferred. The current primary Chemistry Reviewer, Doma 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."*

#### Division Director's Comment

- *I concur with the assessment/recommendation of Dr. Christner.*

### 4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

There were no outstanding Pharmacology/Toxicology issues at the time of the Approvable action, aside from potential 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."*

Dr. Reid also made several recommendations regarding labeling that were subsequently incorporated into final labeling.

#### Division Director's Comment

- *I concur with the recommendation of Dr. Reid.*

### 5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

The primary efficacy and safety Study WHO 97902 was not conducted with the to-be-marketed product, but with two 0.75 mg LNG tablets taken at the same time. The Applicant submitted data from a bridging study (Study 2990) that demonstrated bioequivalence between a single 1.5 LNG tablet (the to-be-marketed product) and the two 0.75 mg LNG tablets that were used in the primary Phase 3 clinical trial.

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

#### Division Director's Comments

- *Acceptable labeling was submitted by the Applicant.*
- *I concur with the conclusion and recommendation of Dr. Kim.*

## 6. CLINICAL MICROBIOLOGY

A microbiology review was not needed for this oral product.

## 7. CLINICAL/STATISTICAL-EFFICACY

A full review and discussion of the efficacy data that were provided in support of approval of LNG 1.5 mg for marketing are contained in the original clinical reviews of the primary Medical Reviewer (Dr. Davis) and the Clinical Team Leader (Dr. Soule), which were both signed on November 22, 2006. Only the major efficacy findings for LNG 1.5 mg are presented in this Summary Review.

### 7.1 Overview of Clinical Program

In the original NDA submission of January, 2006, 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 and were randomized to one of 3 arms – LNG 0.75 mg, administered in 2 doses 12 hours apart, LNG 1.5 mg administered in a single dose, or single dose mifepristone 10 mg. The objectives of the study were to assess for emergency contraception (1) the efficacy of (a) each of 2 dosing regimens for LNG when administered either as 2 doses of 0.75 mg 12 hours apart (i.e., the regimen of Plan B) or as one dose of 1.5 mg (i.e., the regimen of Plan B One-Step) and (b) that of a single dose of 10 mg of mifepristone and (2) whether the same effectiveness would be maintained while extending the initiation of treatment from 72 hours to 120 hours after intercourse.

#### Division Director's Comments

- *Although the study assessed the effectiveness of 3 emergency contraceptive regimens, the clinical reviews focused on the effectiveness of the 2 different dosing regimens for LNG because the Applicant was not seeking approval for mifepristone.*
- *Additionally, although women were randomized if they presented within 120 hours of unprotected intercourse, the Applicant was requesting an indication for use only within 72 hours after unprotected intercourse; therefore, this Memorandum focuses primarily on efficacy when the 2 LNG dosing regimens were initiated within 72 hours after unprotected intercourse.*

Supportive efficacy and safety information was provided based upon the publication of a study conducted in Nigeria comparing the safety and efficacy of the two-dose regimen of LNG 0.75 mg with the single-dose regimen of LNG 1.5 mg.<sup>1</sup> In the Nigerian study, 1,160 women presenting within 72 hours of unprotected intercourse were randomized into one of the 2 treatment regimens. This study, although supportive, was not essential to approval of the single-dose regimen.

In both the WHO and Nigerian studies, women were included on the basis of regular menstrual cycles, unprotected intercourse within 72 hours (120 hours for the WHO study) of enrollment, and agreement to refrain from further intercourse until their next menses had occurred.

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<sup>1</sup> 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.



## 7.2 Primary Clinical Study – WHO Study 97902

### 7.2.1 Efficacy Endpoints and Objectives

The prevention of expected pregnancy was the primary efficacy outcome measure. The proportion of expected pregnancies prevented by the treatment, the prevented fraction (PF), was the primary efficacy variable and was defined as follows:

$$\text{Prevented Fraction} = [1.0 - (\text{Observed pregnancies}/\text{Expected pregnancies})] \times 100$$

The expected number of pregnancies was calculated by multiplying the number of women having unprotected intercourse on each specific day of the menstrual cycle by the estimated probability of conception on that day of the cycle. The cycle day was determined relative to the estimated date of ovulation, which was defined by subtracting 14 days from the expected date of the next menstrual period. The pregnancy rate (PR), or percentage of women who became pregnant, and its 95% confidence interval, also was calculated. No formal statistical comparisons or threshold to determine efficacy were planned for the study.

### 7.2.2 Primary Efficacy Findings

The primary efficacy analysis showed similar effectiveness for the single-dose and two-dose LNG regimens (83.95% and 78.92%, respectively) as assessed by the prevented fraction of expected pregnancies (see Table 1). The overlapping confidence intervals for the two dosing regimens indicate that the difference in prevented fraction of expected pregnancies was not statistically significant.

**Table 1 Prevented Fraction of Pregnancies in WHO Trial 97902 (ITT Population\*)**

LNG Group	N	Observed Pregnancies				Expected Pregnancies #	Prevented Fraction (%) of Expected Pregnancies		
		#	Rate	95% LL	95% UL		PF**	95% LL***	95% UL
<b>Single-Dose</b>	1198	16	1.34	0.77	2.16	99.7	<b>83.95</b>	73.94	90.83
<b>Two-Dose</b>	1183	20	1.69	1.04	2.60	94.9	<b>78.92</b>	67.44	87.12

\* Subjects who enrolled within 72 hrs of unprotected intercourse.

\*\* PF: prevented fraction of expected pregnancies.

\*\*\* LL = lower limit; UL = upper limit

Source: Modified from Table 4 of the original review of the Clinical Team Leader, signed Nov. 22, 2006.

### 7.2.3 Secondary Efficacy Analyses

**Relative Risk of Pregnancy.** A secondary efficacy measure was the relative risk (RR) of pregnancy in women using the single-dose regimen of LNG as compared to the two-dose regimen of LNG. The crude RR was 0.79, with a confidence interval spanning 1.0, indicating no significant difference in the risk of pregnancy between the 2 dosing regimens. The adjusted RR, which controlled for the number of expected pregnancies in each treatment group, was similar (see Table 2).

**Table 2 Relative Risk of Pregnancy in WHO Study 97902 (ITT Population\*)**

LNG Treatment Groups	Crude Ratio with CI			Adjusted Ratio with CI		
	RR	95% LL	95% UL	RR	95% LL	95% UL
<b>Single-Dose vs. Two-Dose</b>	<b>0.7900</b>	0.4114	1.5170	<b>0.7612</b>	0.3690	1.5438

\* Subjects who enrolled within 72 hrs of unprotected intercourse.

Source: Modified from Table 5 of the original review of the Clinical Team Leader, signed Nov. 22, 2006.

#### 7.2.4 FDA Statistical Assessment

In an Addendum, signed on November 21, 2006, to her original statistical review, Dr. Castillo confirmed that she had verified the Applicant's efficacy analyses in the original Application for the subgroup of women presenting for treatment within 72 hours of unprotected intercourse.

#### 7.3 Supportive Clinical Study

In the study conducted in Nigeria (Arowojolu AO et al), 1,160 women were randomized (560 to the two-dose group and 600 to the single-dose group). A total of 42 women (3.6%) were lost to follow-up: 15 (2.7%) in two-dose group and 27 (4.5%) in single-dose group, resulting in a total of 1,118 evaluable women. The protocol for this study was very similar to the WHO Study except that all the women were treated within 72 hours of unprotected intercourse and there was not a third treatment arm. Eleven (11) pregnancies (0.98% overall rate) were reported (4 in the single-dose group and 7 in the two-dose group; see Table 3). The prevented fraction of expected pregnancies was numerically higher in the single-dose group (92.99%) than in the two-dose group (86.80%). For the single-dose regimen compared to the two-dose treatment regimen, the crude relative risk was 0.71 (95% CI 0.32-1.55).

**Table 3 Efficacy Results in ITT Population- Nigerian Trial**

LNG Group	N	Observed Pregnancies				Expected Pregnancies	Prevented Fraction (%) of Expected Pregnancies		
		#	Rate	95% LL	95% UL		#	PF *	95% LL
<b>Single-dose</b>	573	4	0.69	0.02	1.38	57.1	<b>92.99</b>	81.25	97.38
<b>Two-dose</b>	545	7	1.28	0.34	2.20	53.1	<b>86.80</b>	72.07	93.77

\* PF: Prevented fraction of expected pregnancies.

Modified from Table 12 of the primary Medical Review, signed Nov. 22, 2006.

#### Division Director's Comments

- *The findings for the above study conducted in Nigeria are based entirely on the publication. The original datasets and CRFs were not submitted as part of the NDA.*
- *The findings are similar to those of WHO Study 97902. The findings suggest slightly better contraceptive effectiveness for the single-dose regimen.*

#### 7.4 Overall Assessment of Efficacy

The two LNG dosing regimens are highly effective for emergency contraception. The WHO 97902 Study showed that in the ITT population of over 2,700 women, the single-dose 1.5 mg LNG regimen appeared to have slightly better effectiveness (83.95% of expected pregnancies prevented) than the two-dose 0.75 mg LNG regimen (78.92% of expected pregnancies prevented). The difference between the 2 treatment regimens, however, was not statistically

significant. A trend towards lower efficacy with a longer delay in taking LNG after unprotected intercourse was evident when considering the pregnancy rates for the 2 time intervals (0 to 72 hours and 73 to 120 hours after intercourse) for both the single- and two-dose regimens. The study conducted in Nigeria is supportive of the effectiveness of both dosing regimens when LNG is taken within 72 hours of unprotected intercourse.

Stratification of analysis by age in the WHO trial indicated that the single dose regimen was similarly efficacious in women above and below the age of 35. Additional analyses highlighted some potential limitations of the efficacy of LNG as an emergency contraceptive, limitations which are currently stated in prescription labeling for Plan B. The efficacy appears slightly lower in Chinese women than non-Chinese women, for reasons that are not known. The WHO trial also demonstrated a clear decrease in efficacy when treatment is delayed, particularly beyond 72 hours of unprotected intercourse.

Concerning overall efficacy for LNG emergency contraception, it will be important to emphasize the following in labeling:

- Women should take a LNG 1.5 mg tablet as soon as possible after unprotected intercourse or a contraceptive failure and within 72 hours of the event.
- Treatment is for emergency contraception and not for routine contraception.

## **8. SAFETY FINDINGS**

A full review and discussion of the safety data that were provided in support of approval of LNG 1.5 mg for marketing are contained in the original clinical reviews of the primary Medical Reviewer (Dr. Davis) and the Clinical Team Leader (Dr. Soule), which were both signed on November 22, 2006. In this Summary Review, only the major safety findings for LNG 1.5 mg based on the clinical trial data in the original Application are presented, as well as a brief review of postmarketing safety data, primarily for Plan B. The primary Medical Review by Dr. Davis, signed on July 9, 2009, includes an in depth review of the postmarketing safety data submitted in the Applicant's Safety Update.

### **8.1 WHO Study 97902 (Primary Source of Clinical Trial Safety Data)**

In WHO Study 97902, all women who had received at least one dose of study medication were included in the safety analysis. A total of 1,379 women were included in the safety analysis in the LNG single-dose group, and 1,377 women were included in the LNG two-dose group.

#### **8.1.1 Deaths and Other Serious Adverse Events**

There were no deaths in the clinical trial.

In subjects taking LNG, there were 3 reports of serious adverse events during the study. In the LNG single-dose group, 2 serious adverse events were reported: a ruptured corpus luteum cyst and acute appendicitis. In the LNG two-dose group, a single serious adverse event was reported: an ectopic pregnancy.

#### **8.1.2 Common Adverse Events**

A total of 695 women who received the single-dose regimen and 693 women receiving the two-dose regimen experienced at least one adverse event (AE) during the trial. The most

commonly reported AEs included vaginal bleeding, nausea, lower abdominal pain, and fatigue (see Table 4).

**Table 4 Number (%) of Subjects Reporting Specific Adverse Events in WHO Study 97902**

Adverse event	Single-dose LNG Group N = 1,379		Two-dose LNG Group 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: Table 15, from the primary Medical Review of the original NDA submission, signed November 22, 2006.

**Division Director's Comments**

- *The incidence of common AEs did not differ substantially between the 2 LNG treatment regimens.*
- *The overall frequency of AEs and the types of common AEs do not raise any safety concerns and are to be expected based on previous clinical studies with Plan B (2 doses of LNG, separated by 12 hours).*

**8.1.3 Alteration in Menstrual Bleeding Patterns**

Use of LNG for emergency contraception can result in an alteration in the timing of the first post treatment menses. In the WHO study, more than half of all subjects experienced menses within two days of the expected time. In each treatment group, only 4.5% of women experienced a delay of 7 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. In the LNG single-dose group, 77% of subjects reported their first post-treatment menses as "similar" to their usual menses. Twelve percent (12%) reported bleeding that was "more" (11%) or "much more" (1%), and 11% reported bleeding as "less" than normal menses.

**8.2 Nigerian Study (Supportive Safety Data)**

In the clinical trial conducted in Nigeria, the most frequently reported adverse events were nausea, headache, lower abdominal pain, heavy menses, breast tenderness, dizziness, and vomiting (see Table 5).

**Table 5 Percentages of Women Reporting Specific Adverse Events (Nigerian Study)**

Adverse Event	LNG Two-Dose Group N=518	LNG Single-dose Group N=544
Nausea	22.9	24.3
Headache	14.5	21.3
Lower abdominal pain	18.3	15.6
Heavy menses	10.5	15.5
Breast tenderness	8.8	12.9
Dizziness	13.9	12.6
Vomiting	8.4	7.8

Source: Table 13, review of Clinical Team Leader, signed November 22, 2006.

#### **Division Director's Comment**

- *Although the percentage of subjects reporting specific common adverse events was higher in the Nigerian Study than in the considerably larger WHO study, the findings from the Nigerian study do not raise any new safety concerns regarding either the single-dose or two-dose treatment regimens.*

#### **8.3 Safety Updates**

##### **8.3.1 Safety Update (Original NDA Submission)**

In the original NDA, a safety update was submitted by the Applicant providing a Periodic Safety Update Report (PSUR) for the period January 1, 2006, to June 30, 2006, for both the two-dose 0.75 mg and the single-dose 1.5 mg LNG products used for emergency contraception. The Clinical Team Leader stated the following in her review:

*"Gedeon Richter estimates that over the reporting period, over \_\_\_\_\_ uses of LNG emergency contraception occurred; more than \_\_\_\_\_ in the 60 countries in which the two-dose regimen is marketed and \_\_\_\_\_ in the 21 countries in which the single dose regimen is 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 pruritus. The remaining reports are of non-serious, listed, unconfirmed, and 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 LNG for emergency contraception found in the FDA's Adverse Event Reporting System (AERS) database since the approval of Plan B in July 1999. These data also were reviewed by the primary Medical Reviewer (Dr. Davis) who made the following concluding comment:

*"Based on the information provided by the FDA's Office of Surveillance and Epidemiology (OSE) and data previously reviewed by DRUP, the benefits of two dose 0.75 mg levonorgestrel (Plan B) use as an emergency contraceptive continue to outweigh the known risks of the product. The findings raise no concerns regarding the safety of the Plan B levonorgestrel product."*

In my Division Director Memorandum of November 22, 2006, I made the following statements:

*"I have also reviewed the September 2006 data provided by OSE from the FDA's AERS database for Plan B. Based on my review, I concur with Dr. Davis's assessment that the findings raise no concerns regarding the safety of the Plan B LNG product."*

*"The Applicant's Safety Update did not differentiate between events related to the one-dose regimen versus the two-dose regimen. Because there are no clinical trial data that suggest that there are any differences in the safety profiles of the two different dosing regimens, the post marketing safety data from the two-dose regimen also should be reflective of the post marketing safety profile of the single-dose regimen."*

*"Similarly, data from the AERS safety database for Plan B should be reflective of the likely post marketing safety profile for the single-dose product."*

### **8.3.2 Safety Update (Complete Response)**

The Applicant's most recent Safety Update also included safety information for both Plan B (two-dose product) and LNG 1.5 mg (Plan B One-Step). In the update, the Applicant stated that there was one ongoing trial with LNG 1.5 mg (Study DR-LEV-302) that was enrolling females age 17 years and younger. The Applicant further stated that *"as of June 9, 2009, there "have been no deaths, no serious adverse events, and no discontinuations due to adverse events in the ongoing clinical trial DR-LEV-302."*

Also contained in the June 9, 2009, Safety Update were (1) excerpts from the most recent Periodic Adverse Drug Experience Report (PADER) for Plan B (two-dose product) that had previously has been submitted to NDA 21-045 in August, 2008, by the Applicant and (2) the most recent international PSUR, prepared by Gedeon Richter, the manufacturer of both Plan B and LNG 1.5 mg. Gedeon Richter is the distributor and/or manufacturer for virtually identical LNG products in a number of non-U.S. countries. The Safety Update also included the statement that *"neither product has been withdrawn from marketing in any country for reasons of safety or efficacy."*

Dr. Davis has thoroughly summarized and discussed the findings from both the PADER and the PSUR in his primary Medical Review. A brief overview of the findings, based on Dr. Davis' review, is provided.

#### Periodic Adverse Drug Experience Report for Plan B (Reporting Period: July 1, 2007 through June 30, 2008).

During the Reporting Period, Duramed estimated that approximately \_\_\_\_\_ U.S. patients were exposed to Plan B. During this period, there were 9,029 individual case reports describing 15,432 adverse events. According to the primary Medical Review, only 7 of these adverse events, involving 5 individuals, were listed as both serious and medically confirmed. These 7 reports included 2 reports of ectopic pregnancy and one report each of spontaneous abortion, missed abortion, blood in urine, pancreatitis, and cytomegalovirus infection (CMV). The adverse event of "blood in urine" was reported in association with one of the cases of ectopic pregnancy, where vaginal bleeding can commonly contaminate a urine specimen. The adverse event of "pancreatitis" was considered secondary to the CMV infection (both events being reported in a single case). The use of Plan B was not considered in the report to be related to either of the adverse events. Of the 10 most commonly reported AEs during the Reporting Period, 8 are already described in labeling

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(i.e., change/irregular menses, nausea, abdominal pain, vomiting, headache, oligomenorrhea, dizziness, and fatigue.

**Division Director's Comments**

- *Dysmenorrhea and pelvic pain, not presently included in product labeling for Plan B, will be added to the Postmarketing Experience section of the to-be-approved labeling for both Plan B and Plan B One-Step based, in part, on the findings from the Applicant's pharmacovigilance program for Plan B.*
- *The Applicant also plans to conduct close monitoring for several specific AEs that were reported, but not medically confirmed, during the last reporting period. These include cases of hypersensitivity (4 reports), loss of consciousness (7 reports), syncope (6 reports), dyspnea (27 reports), and erythema nodosum (one report).*

PSUR for Two-Dose and One-Dose LNG Products (Reporting Period: July 1, 2008 through December 31, 2008). During the Reporting Period, Gedeon Richter estimated that there were approximately \_\_\_\_\_ and \_\_\_\_\_ uses of the two-dose and single-dose products, respectively. According to Dr. Davis' review, 528 adverse reactions, involving 230 individual cases, were received by Gedeon Richter during the 6-month reference period. The 3 most commonly reported adverse events were spontaneous abortion, irregular bleeding, and delayed menstruation.

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**Division Director's Comments**

- *Irregular bleeding and delayed menstruation are expected events among users of LNG emergency contraception (i.e., Plan B).*
- *Reports of spontaneous abortion following Plan B treatment failures do not constitute a safety concern because approximately 20% of all pregnancies naturally end by spontaneous abortion.*
- *Dr. Davis made the following statement in his review: "In summary, this reviewer does not see any new safety signals in the data reported by Gedeon Richter in their 20<sup>th</sup> PSUR covering well over \_\_\_\_\_ uses of levonorgestrel for emergency contraception." I concur with Dr. Davis' assessment.*

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**8.3.3 OSE Safety Reviews**

Since DRUP issued the Approvable letter for LNG 1.5 mg in November, 2006, the Division of Pharmacovigilance II (DPV II, formerly the Division of Adverse Event Analysis II) has conducted 2 safety reviews for Plan B based on the safety reports in FDA's AERS database. The most recent of the reviews searched for (1) all adverse events entered into the AERS database from March 12, 2008 (the cut-off date of the previous review) through May 14, 2009, for all users of Plan B regardless of their age and (2) all adverse events entered into the AERS database for females from 1999 (the year of approval of Plan B) through May 14, 2009, for users of Plan B who were less than 18 years of age at the time of their use of the product.

The DPV II review identified a total of 73 cases that had been received by FDA since March 12, 2008. Only 13 cases were identified for users of Plan B younger than 18 years of age since the 1999 approval of the product. These latter 13 cases involved non-serious and/or

labeled adverse events or were assessed as unrelated or having an unknown relationship to Plan B.

**Division Director's Comments**

- *Since January 2007, there have been approximately \_\_\_\_\_ prescriptions filled for Plan B in this population annually. Most of these prescriptions were likely for females younger than 18 years of age because Plan B is available without prescription for women age 18 years and older.*
- *Dr. Davis stated that none of these 13 reports in females younger than 18 years of age raised new safety issues, and I agree with his assessment.*

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The Executive Summary of the DPV II Review (dated June 19, 2009) included the following statements:

*"... 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."*

**Division Director's Comments**

- *The comprehensive reviews by DPV II in both 2008 and 2009 did not raise any new safety concerns that would impact on the overall favorable benefit/risk profile of Plan B or warrant any changes in labeling.*
- *In the 2008 Review, however, DPV II noted a possible safety signal for syncope and loss of consciousness in users of Plan B and stated that there was a "suggestion of a possible temporal relationship with Plan B administration in this small case series." DRUP medical officers agreed that DPV II should continue to monitor for these adverse events but did not believe that either syncope or loss of conscious should be added to labeling at this time because of the small number of cases and lack of adequate documentation. Both DPV II and the Applicant, as part of ongoing pharmacovigilance, will continue to monitor for these adverse events to better assess their possible relationship to treatment with Plan B and Plan B One-Step after its approval for marketing.*

Since approval of Plan B in 1999, only 2 fatalities have been reported in U.S. patients. One of the cases was the death of a 21-year-old woman with extensive concomitant drug use, for whom OSE believed that the death was unlikely to be related to the use of Plan B. The other case was a death of unknown cause 3 days after birth in a premature infant born at 5 months gestation to a 31-year -old woman. According to the OSE review, the woman took her first dose of Plan B on an unknown date in December 2005 and became pregnant afterwards. There is no more information on this case

**8.4 Overall Assessment of Safety**

Based on the clinical trial data from the primary safety study in this NDA (WHO Study 97902) and supportive safety data from the clinical trial in Nigeria (Arowojolu AO et al), the safety profile for the single-dose regimen of 1.5 mg LNG is very similar to that seen with the approved two-dose regimen (0.75 mg LNG per dose taken 12 hours apart). Furthermore, the safety data



for each LNG dosing regimen in these studies do not raise any concerns regarding the overall safety profile for LNG when used for emergency contraception.

Based on the safety data from (1) primary Study 97902 and the supportive Study conducted in Nigeria and (2) the respective pharmacokinetic profiles for LNG when administered as either a single 1.5 mg dose or 2 doses of 0.75 mg separated by 12 hours, it is likely that the postmarketing safety profiles for Plan B One-Step (LNG 1.5 mg) and Plan B (LNG 0.75 mg x 2) will be very similar. FDA's Office of Surveillance and Epidemiology has conducted periodic review of the safety data for Plan B in FDA's AERS database since the approval of the product in 1999. These periodic reviews have not identified any worrisome safety signals that would alter my assessment that the overall benefit/risk profile for Plan B remains favorable. Because there are no clinical trial data that suggest that there are any differences in the safety profiles of the 2 different LNG dosing regimens, the post marketing safety data from the two-dose regimen (i.e., Plan B) should be reflective of the likely post marketing safety profile for the single-dose regimen (i.e., Plan B One-Step).

These postmarketing safety reviews, primarily based on Plan B, have identified a possible emerging safety signal for rare cases of syncope and loss of consciousness in users of Plan B. DRUP medical reviewers and I do not believe that these events have been sufficiently well characterized to warrant inclusion in labeling for either Plan B or Plan B One-Step at this time. Both OSE and the Applicant will continue pharmacovigilance surveillance for these and other adverse events.

#### 8.5 CARE Program

The Applicant stated in the Complete Response that they intend to conduct a CARE (Convenient Access, Responsible Education) Program for Plan B One-Step that will be virtually identical to the ongoing CARE program for Plan B. According to the Applicant, the CARE Program (quoted below directly from the Applicant's submission) will include the following 4 elements:

- Labeling/Packaging/Informational toll free number (to provide essential information to consumers in an accessible, easy to understand format. The Plan B One-Step packaging is designed to meet both prescription and OTC requirements.)
- Education (to provide information intended to educate physicians, pharmacists, pharmacy staff, nurse practitioners, and patients.)
- Distribution (to ensure that Plan B One-Step will be available only to licensed drug wholesalers, retail operations with pharmacy services and clinics with licensed healthcare practitioners, and to successfully facilitate the Plan B One-Step prescription-only age requirement.)
- Monitoring (to evaluate the effectiveness of the program by determining if the age restriction is understood by all audiences and is properly being adhered to.)

#### Division Director's Comments

- *The approval of Plan B as a dual Rx/OTC product included a postmarketing agreement to conduct the CARE Program, in part, 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 of Plan B and has reported the findings to the FDA. The most recent results have demonstrated excellent*

*levels of compliance with the dual marketing age restrictions. Both the primary Medical Reviewer (Dr. Davis) and the Clinical Team Leader (Dr. Soule) do not believe that Plan B One-Step requires a CARE Program, based on the findings from the monitoring component of the ongoing CARE Program for Plan B.*

- *Although I concur that there is a high likelihood that many components of the CARE Program may not be needed, there is merit to the Applicant's conducting the CARE Program for at least the first one or two years after launch of Plan B One-Step. Among the benefits of the Program will be the collection of data to support the decision by DNCE that lowering the age to 17 years and older for OTC availability for Plan B and Plan B One-Step will not negatively impact on the ability of pharmacies to limit the availability of these products to prescription-only status for females younger than 17 years of age.*
- *Any future modifications of the Program must be discussed with the FDA prior to its implementation to ensure that the modifications do not alter the objectives of the program and that they are not of a promotional nature.*

#### **8.6 Justification for Reduction in Age for Nonprescription Availability**

Dr. Leonard-Segal, Director of DNCE, made the following statement in a letter to Duramed Research, concerning a lowering of the age for nonprescription availability for Plan B:

*"...I have now considered whether the enforceability concerns expressed by the Commissioner necessitate an age restriction to women 18 years of age and older for nonprescription use as opposed to a restriction to women 17 years of age and older. I am unaware of data that support a distinction between ages 17 and 18 in terms of enforceability of an age restriction. Data recently submitted by you regarding your Convenient Access Responsible Education (CARE) Program, under which you have monitored compliance with the current prescription age requirement, support the fact that pharmacists do check identification for the age restriction as it exists today. I have no reason to doubt that pharmacists are capable of accurately determining the age of women seeking to purchase Plan B without a prescription by reviewing identification and providing Plan B according to the conditions of approval as related to age. I therefore conclude that Plan B may be made available to women 17 years and older without a prescription."*

#### **Division Director's Comments**

- *I concur with Dr. Leonard-Segal's rationale and decision that Plan B could be made available to women 17 years and older without a prescription.*
- *The same rationale also applies to nonprescription availability for LNG 1.5 mg (Plan B One-Step) and supports the Applicant's request that LNG 1.5 mg also be available to women 17 years and older without a prescription.*

### **9. ADVISORY COMMITTEE MEETING**

The original NDA Supplement requesting that Plan B be switched from prescription-only availability to OTC availability was discussed in 2003 at a joint Advisory Committee meeting, which included members from both the Reproductive Health Drugs and Nonprescription Drugs Advisory Committees. The joint Committee recommended by a vote of 23 to 4 that Plan B be

switched from prescription-only availability to non-prescription (OTC) availability. The recommendation was not contingent on any age or distribution restrictions.

DRUP determined that an Advisory Committee meeting to discuss the current Application for LNG 1.5 mg was not needed because NDA 21-988 did not raise any new safety or efficacy issues.

## **10. PEDIATRICS**

The Applicant requested a partial waiver and partial extrapolation for pediatric studies. DRUP 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 with DRUP's recommendation.

## **11. OTHER RELEVANT REGULATORY ISSUES**

There are no unresolved regulatory issues.

## **12. LABELING**

### **12.1 Product Name**

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.

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### **12.2 Prescription Labeling**

Since the first review cycle, the Physicians Labeling Rule (PLR) has become the standard for labeling format. The Applicant submitted labeling in PLR format, which represented a major change in format, although only minor change in content, as compared to the current label for the approved Plan B product. New sections that exist in PLR labeling, but were not previously included in the Plan B label, include:

- Highlights
- Dosage Forms and Strengths
- Warnings and Precautions (formerly two separate sections)
- A Postmarketing subsection within Adverse Reactions
- Patient Counseling Information

In reviewing the proposed labeling submitted by the Applicant in the amended Complete Response submission, several items were negotiated with the Applicant, with resolution reached that was satisfactory to both DRUP and the Applicant. Among these were:

- Instructions for healthcare providers and patients in case of vomiting within two hours after taking the tablet. The labeling directed toward healthcare providers states "consideration should be given to repeating the dose," while that for patients states "immediately contact your healthcare provider to discuss whether to take another tablet."

- Inclusion of postmarketing adverse event data based on Plan B events in a Postmarketing Experience subsection of the Adverse Reactions section of Plan B One-Step. Postmarketing adverse events are likely to be similar in users of either product.
- Removal of the statement \_\_\_\_\_ as a contraindication to conform with PLR formatting.
- Revision and updating of the Drug Interactions section (formerly a subsection in the Precautions section).
- Change (compared to previously approved labeling for Plan B) from 16 years to 17 years in age to be listed in the Pediatric Use subsection to better conform with the definition of the pediatric population. The revised sentence (Section 8.4 of to-be-approved labeling) will read:

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*“Safety and efficacy are expected to be the same for postpubertal adolescents less than 17 years and for users 17 years and older.”*

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.

Final acceptable prescription labeling was received from the Applicant on July 9, 2009.

### **12.3 OTC and Carton and Container Labeling**

The Consumer Information Leaflet (CIL) was reviewed by the Office of Nonprescription Products and agreement was reached with the Applicant on July 8, 2009. There is no separate patient package insert for the prescription product because all consumers receive the CIL.

Carton and container labeling was reviewed by DMEPA, by the CMC reviewer, and the Office of Nonprescription Products. All requested changes were incorporated by the Applicant.

## **13. DECISION/ACTION/BENEFIT RISK ASSESSMENT**

### **13.1 Regulatory Action**

The Applicant has provided sufficient data for me to conclude that a single 1.5 mg levonorgestrel tablet (Plan B One-Step), taken within 72 hours following unprotected intercourse or a known or suspected contraceptive failure, is safe and effective to reduce the likelihood of an unplanned pregnancy. I therefore recommend that Plan B One-Step be approved for marketing. Based on the Applicant's request, I also recommend that Plan B One-Step be available without prescription (i.e., OTC) for women 17 years of age and older and by prescription-only for females younger than 17 years of age.

### **13.2 Benefit/Risk Assessment**

The Applicant has provided sufficient data for me to conclude that a single 1.5 mg levonorgestrel tablet (Plan B One-Step), taken within 72 hours following unprotected intercourse or a known or suspected contraceptive failure, is safe and effective to reduce the likelihood of an unplanned pregnancy. Based on the safety data from (1) primary Study 97902 and the supportive Study reported in the publication by Arowojolu AO et al and (2) the respective pharmacokinetic profiles for LNG when administered as either a single 1.5 mg dose or 2 doses of 0.75 mg separated by 12 hours, it likely that the postmarketing safety profiles for Plan B One-Step

(LNG 1.5 mg) and Plan B (LNG 0.75 mg x 2 doses) will be very similar. FDA's Office of Surveillance and Epidemiology (OSE) has conducted periodic reviews of the safety data for Plan B contained in FDA's AERS database since approval of the product for marketing in 1999. These periodic reviews have not identified any worrisome safety signals that would alter my assessment that (1) the overall benefit/risk profile for Plan B remains favorable and (2) the overall benefit/risk profile for Plan B One-Step will likely be similar to that for Plan B.

In my previous Memo for NDA 21-998, based on the original NDA submission and signed on November 22, 2006, I stated that "I believe that levonorgestrel 1.5 mg tablets (as well as Plan B) should be available as a nonprescription product without any age restriction for all postmenarcheal women." I continue to believe that levonorgestrel 1.5 mg tablet (Plan B One-Step) meets the regulatory criteria for nonprescription (OTC) sale and use by postmenarcheal women of all ages. The Applicant, however, is not seeking full nonprescription marketing status for Plan B One-Step. Therefore, to make available an emergency contraceptive product that has a simpler dosing regimen over that of the currently approved product, I am recommending that Plan B One-Step be available without prescription (OTC) for women 17 years of age and older and by prescription-only for women younger than 17 years of age.

### **13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

No significant safety signals have been identified in (1) data from the 2 clinical trials that support the safety and efficacy of Plan B One-Step, (2) postmarketing U.S. safety data for Plan B, and (3) non-U.S. postmarketing safety data provided by Gedeon Richter (the manufacturer of Plan B One-Step); therefore, a postmarketing Risk Evaluation and Mitigation Strategy (REMS) is not warranted.

### **13.4 Recommendation for other Postmarketing Requirements and Commitments**

None. The Applicant has volunteered to conduct a modified CARE (Convenient Access, Responsible Education) Program for Plan B One-Step that will be very similar to the ongoing CARE Program for Plan B. The Program, as proposed in their submission of July 7, 2009, is acceptable.

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/s/

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Scott Monroe  
7/10/2009 10:35:38 AM  
MEDICAL OFFICER

## Summary Review for Regulatory Action

<b>Date</b>	July 9, 2009
<b>From</b>	Andrea Leonard-Segal, M.D., M.S Director, Division of Nonprescription Clinical Evaluation (DNCE)
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	21-998
<b>Supplement #</b>	
<b>Applicant Name</b>	Duramed Pharmaceuticals Inc.
<b>Date of Submission</b>	January 12, 2009
<b>PDUFA Goal Date</b>	July 12, 2009
<b>Proprietary Name / Established (USAN) Name</b>	Plan B® One-Step / levonorgestrel
<b>Dosage Forms / Strength</b>	Tablet 1.5 mg
<b>Proposed Indication(s)</b>	1. OTC indication: Reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control) 2. Prescription indication: Plan B® One-Step is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the tablet should be taken as soon as possible within 72 hours of intercourse.
<b>Action/Recommended Action</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including: Medical Officer Review, DRUP/ Medical Officer DNCE and Clinical Team Leader, DNCE	Daniel Davis, M.D., M.P.H. / Christina Chang, M.D., M.P.H. and Lesley-Anne Furlong, M.D.
Statistical Review	Sonia Castillo, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Lynnda Reid, Ph.D.
CMC Review/OBP Review	Monica Cooper, Ph.D, Donna Christner Ph.D, Moo-Jhong Rhee, Ph.D.,
Microbiology Review	N/A
Clinical Pharmacology Review	Myong-Jin Kim, Ph.D and Ameeta Parekh, Ph.D.
DDMAC	Janice Maniwang, PharmD and Carrie Newcomer, PharmD.
DSI	N/A
CDTL Review	Lisa Soule, M.D.
OSE/DMETS	LaToya S. Toombs, PharmD, Denise Toyer PharmD, and Carol Holquist, PharmD
OSE/DPV II	Melissa Truffa, RPh, Robert Boucher, MD, MPS, Gerald Dal Pan, MD, MHS
DNRD Labeling Reviewers	Arlene Solbeck M.S., Marina Chang, R.Ph.
DRUP Division Director Reviews	Scott Monroe, M.D.

## **1. Introduction**

Levonorgestrel is a second generation progestin derived from norgestrel. Since 1996, it has been an active ingredient in many approved contraceptive drugs in the United States (U.S.). Among the approved levonorgestrel-containing products is Plan B®, levonorgestrel 0.75 mg, an orally administered emergency contraceptive. Plan B® was initially approved in the United States as a prescription-only emergency contraceptive on July 28, 1999. The treatment regimen for Plan B® consists of two doses; the first 0.75 mg tablet is to be taken as soon as possible within 72 hours of having unprotected sexual intercourse or a known or suspected contraceptive failure and the second is to be taken 12 hours later. This product was approved for over-the-counter (OTC) marketing for women ages 18 and above on August 24, 2006 and remained prescription for females 17 years of age and under via NDA 21-045/S-011. The product was approved as a single package configuration for dual prescription and nonprescription (OTC) marketing. Since the carton bears the statement “Rx only for age 17 and younger,” the product is required to be kept behind the pharmacy counter and/or distributed by licensed practitioners.

The exact mechanism of action for levonorgestrel as an emergency contraceptive is not known. Levonorgestrel it is thought to act by delaying ovulation post-coitally by impairing follicular maturation and disrupting mechanisms involved in the luteinizing hormone surge. Post-ovulatory mechanisms of action may include such things as interference with fertilization resulting from changes in cervical mucus and uterine fluid that interfere with sperm penetration and migration. Endometrial desynchronization may interfere with implantation of a fertilized egg; however, levonorgestrel is not effective once implantation has begun.

NDA 21-998 was submitted to support the use of levonorgestrel 1.5 mg as a single dose (one tablet) regimen to be taken as soon as possible after having unprotected sexual intercourse (but within 72 hours). The sponsor submitted NDA 21-998 on January 24, 2006 requesting prescription status for this product for females of all ages. On November 22, 2006, the FDA issued Duramed Research, Inc., the U.S. agent for the applicant at the time, Gedeon Richter, Ltd, an “approvable” action letter. The letter cited the following deficiency in the application:

*“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.”*

The sponsor was also told to submit a safety update as described in 21 CFR 314.50(d)(5)(vi)(b). On January 12, 2009, FDA acknowledged receipt of Duramed’s complete response to the approvable letter.



## 2. Background

Dr. Lisa Soule, in her Division of Urologic and Reproductive Products (DRUP) team leader memorandum dated November 22, 2006, nicely distills the complex Plan B® regulatory history, the denouement of which was the approval of the partial OTC switch of Plan B® (levonorgestrel 0.75 mg) for women 18 years and older and the continuation of the prescription marketing for the population 17 years and younger. Refer to Dr. Soule's memorandum for that history. I will highlight certain parts of the regulatory history here.

In his August 26, 2005 memorandum on Plan B®, Dr. Steven Galson, Director, CDER, concluded that the data supported OTC use of Plan B® by women aged 17 years and older, but not by females ages 16 years and younger. In his memorandum dated August 23, 2006, Dr. Andrew von Eschenbach, then Acting FDA Commissioner, concurred that the scientific data supported an OTC indication for women aged 17 years and older. However, he stated the following:

*"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. The state-regulated pharmacies that will be dispensing Plan B® under Barr's voluntary CARE<sup>SM</sup> program (as well as society as a whole) are more familiar with 18 as a cutoff age. I understand that in all 50 states, 18 is the age of majority (i.e., the legal delineation between minor and adult), and retail outlets, including pharmacies, are familiar with using 18 as the age restriction for the sale of certain products.....This approach builds on well-established state and private-sector infrastructures to restrict certain products to consumers 18 and older.....Here, Barr's CARE<sup>SM</sup> program specifically utilizes state-licensed pharmacies to implement its restricted distribution plan. Given this fact, and the existing experience pharmacies have enforcing the age-based restriction of 18, I have determined that to best protect and promote the public health non-prescription Plan B® should be available for ages 18 and above."*

The Convenient Access, Responsible Education Program (CARE<sup>SM</sup>) was constructed by the applicant to help ensure that when Plan B® was OTC it would be used responsibly and appropriately.

The core elements of the CARE<sup>SM</sup> Program follow:

- Labeling/Packaging/Informational toll free number to provide essential information to consumers in an accessible, easy to understand format. The packaging is designed to meet both prescription and OTC requirements.
- Education of healthcare providers and educational materials that healthcare providers can supply to their patients to stimulate discussion. Educational initiatives focus on clearly instructing all audiences on the age requirement that will require those ages 17 years and younger to obtain a prescription for Plan B®.
- Distribution to ensure that Plan B® is available only to licensed drug wholesalers, retail operations with pharmacy services, and clinics with licensed healthcare practitioners, and to successfully facilitate the Plan B® prescription-only age requirement. These settings will also provide easy access by the consumer to a

pharmacist or other healthcare professional should questions arise. Plan B® is not sold, for example, in convenience stores and gas stations.

- **Monitoring Plan** to evaluate the effectiveness of the program by determining if stakeholders understand and adhere to the age restriction. Adjustments to the program will be made as deemed appropriate by the “Point-of-Purchase Monitoring Program” that has been in place in 10 states (400 pharmacies) and overseen by a private contractor.

The CARE<sup>SM</sup> Program has been ongoing since the partial OTC switch was approved and the sponsor has submitted reports on the program which Dr. Daniel Davis (Medical Officer, DRUP) and Dr. Lisa Soule have reviewed. Initially, Duramed provided reports on the program every 6 months and then annually. The reviewers concluded that pharmacy compliance rates with the Monitoring Plan have ranged between 94 – 99% and that the program’s objectives have been accomplished. The data showed that Plan B® is available only with the pharmacist and that enforcement based upon age is occurring; pharmacists do check the ages of women who request to purchase Plan B® OTC. In the conclusion to his March 2009 review, Dr. Davis wrote:

*“It is my opinion that the CARE<sup>SM</sup> Program and Point-of-Purchase Monitoring Program have successfully focused on and accomplished the four core elements of the company’s objectives. To continue the program for another year as already planned would be ideal.”*

He recommended:

*“The CARE<sup>SM</sup> Program should continue as planned with annual reporting. Future review of this program should be transferred to the appropriate Division within the Office of Nonprescription Drugs.”*

On April 1, 2009, Dr. Davis wrote an addendum to the March 2009 review providing a clarifying comment about his conclusion and recommendation regarding the CARE<sup>SM</sup> Program:

*“Since the plan proposed by the sponsor was to continue for another year, I stated it should continue. In fact, I do not believe that the program is necessary at this time or would provide any further useful information, especially since we believe that no age restriction is needed for this product to go safely over-the-counter.”*

On March 23, 2009, the U.S. Federal District Court Judge Edward Korman (in the case of *Tummino v. von Eschenbach et al*) issued an order directing the FDA to permit Duramed to make Plan B® available to women ages 17 years and older without a prescription within 30 days. In addition, he ordered FDA to reconsider whether to approve Plan B® OTC without age or point-of-sale restriction.

On April 21, 2009, in a letter to Duramed in alignment with the court order and over my signature, FDA said,

*"As you were advised in a letter dated August 26, 2005, the Center for Drug Evaluation and Research concluded that the available scientific data were sufficient to support the safe use of Plan B as a nonprescription product for women who are 17 years or older. When FDA made the determination in 2006 to approve nonprescription availability for women 18 years or older, the reason provided for not approving nonprescription access for 17-year-old women was a concern expressed by the Commissioner about the ability of pharmacies (and thus their professional staffs) to enforce the age restriction with respect to purchases by women under age 17 without a prescription.*

*The Center has been authorized to handle this application using the same procedures as for other drugs, as described in the current delegation procedures. Therefore, as the Division Director, I have now considered whether the enforceability concerns expressed by the Commissioner necessitate an age restriction to women 18 years of age and older for nonprescription use as opposed to a restriction to women 17 years of age and older. I am unaware of data that support a distinction between ages 17 and 18 in terms of enforceability of an age restriction. Data recently submitted by you regarding your Convenient Access, Responsible Education (CARE) program, under which you have monitored compliance with the current prescription age requirement, support the fact that pharmacists do check identification for the age restriction as it exists today. I have no reason to doubt that pharmacists are capable of accurately determining the age of women seeking to purchase Plan B without a prescription by reviewing identification and providing Plan B according to the conditions of approval as related to age. I therefore conclude that Plan B may be made available to women 17 years and older without a prescription."*

The letter also said that if Duramed wanted to pursue marketing of Plan B® for women 17 years of age and older without a prescription but prescription only for women 16 years and older, they would need to submit revised draft labeling as a prior approval efficacy supplement to NDA 21-045 that would allow for this change in population.

In the letter, I also told Duramed that if they wanted to pursue the marketing of Plan B® for women 17 years of age and older without a prescription, or other options for marketing Plan B®, that FDA encouraged a meeting to discuss necessary labeling revisions and the content of any submission(s).

On June 1, 2009, Duramed met with FDA to discuss the pathway to a full OTC switch for both the Plan B® and Plan B® One-Step products. At that meeting, Duramed explained that any future drug development plans would be dependent upon the decisions of Teva Women's Health Research, Inc. management. Duramed stated that any decision regarding changes to the labeled population, beyond an OTC switch for women 17 years of age, would occur after the July 12, 2009 PDUFA goal date for NDA 21-998. FDA and Duramed agreed that, for NDA 21-045, the sponsor would provide an efficacy supplement with revised labeling and a safety update to support OTC access down to 17 years of age. Similarly, the sponsor would amend NDA 21-998 for Plan B® One-Step by providing revised labeling for OTC access to 17 years of age and also the requisite safety update. Within two weeks, Duramed submitted all of this material.

### **3. CMC/ Device**

In their 2006 review, the chemistry reviewers, Drs. Monica Cooper and Moo-Jhong Rhee, noted that the manufacturing processes, specifications, and facilities were adequate to assure the quality of the drug product. During the first review cycle chemists recommended that this application could be approved with no Phase IV commitments.

On June 16, 2009, Drs. Donna Christner and Moo-Jhong Rhee completed their review of Duramed's complete response submission to the approvable action letter. The sponsor provided two cartons (one OTC and one prescription) for review and additional stability data on the package as supportive evidence for their requested 24-month expiry. The chemists state that the Office of Compliance has made an overall acceptable recommendation for all manufacturing and testing sites. They also state that the labeling and stability data are adequate. The chemists concluded that the NDA can be approved from the CMC perspective.

### **4. Nonclinical Pharmacology/Toxicology**

There are no outstanding issues related to pharmacology and toxicology. Dr. Lynnda Reid noted that no new pharmacology/toxicology studies were submitted with this application. But, Dr. Reid commented in her review that relevant toxicology data are available in the published scientific literature and that because of the long history of clinical use of levonorgestrel, there are no perceived new safety concerns related to a single dose of 1.5 mg.

Dr. Reid wrote that levonorgestrel has a toxicological profile similar to most other progestins in oral contraceptives. Progestins are generally nontoxic even at fairly high doses when administered over a short period of time. Doses used in pre-clinical studies were > 5000 mg/kg in rodent single dose studies, up to 25 mg/kg/day in rats for one year, up to 0.125 mg/kg/day in dogs for seven years, and 1 mg/kg/day in monkeys for 10 years. Another study exposed monkeys with up to 2.5 mg/kg/day for one year. The acute 5000 mg/kg dose in rodents is greater than 10,000 times the proposed dose of 1.5 mg in humans. Based upon body surface area, the chronic dose animal exposures range from 2.5 to 150 times the proposed human exposure. Teratology studies using doses up to 25 mg/kg in rabbits and 50 mg/kg in rats were negative. Genetic toxicology, carcinogenicity, and reproductive toxicology studies have been negative.

### **5. Clinical Pharmacology/Biopharmaceutics**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (Drs. Myong-Jin Kim and Ameeta Parekh) found the two pivotal bioavailability/bioequivalence studies acceptable. One study (#2990) compared the bioavailability of one levonorgestrel 1.5 mg tablet to the bioavailability of the same single-dose from two Plan B® 0.75 mg tablets in 30 healthy women. The 1.5 mg tablets do not contain gelatin as an inactive ingredient in their formulation; the 0.75 mg tablets do contain gelatin. Bioequivalence was established in this study. The  $T_{max}$  for levonorgestrel 1.5 mg is 1.67 hours (range 1.00 – 4.00 hours) and for levonorgestrel 0.75 mg x 2 is 1.33 hours (range 1.00 – 3.00 hours) as demonstrated in the 30 healthy women under fasting conditions.

The second study (#02162) compared the single-dose bioavailability from one levonorgestrel 1.5 mg tablet to that of two levonorgestrel 0.75 mg tablets administered 12 hours apart in 15 healthy women. In this study, the  $C_{max}$  of the single dose of levonorgestrel 1.5 mg was higher (ratio of means 134.07%) under fasting conditions than the comparator, and but the AUC was within the bioequivalence range of 80 – 125%. The clinical safety data (see below) indicate that this slightly higher  $C_{max}$  is not a clinical concern. Additionally, as Dr. Davis states, the single dose levonorgestrel product is approved in other countries and no precautions or warning relative to the higher  $C_{max}$  appears in the labeling of those products. In this study (#02162) the median  $T_{max}$  for levonorgestrel 1.5 mg and for levonorgestrel 0.75 mg tablets were identical, 2.00 hours.

A third study, World Health Organization/Human Reproductive Program Study WHO/HRP 97902, was a double-blind, randomized, 15-center (family planning clinics) study in 4136 healthy women in ten countries (non-U.S.) to compare the safety and efficacy of levonorgestrel 1.5 mg taken once to the currently approved 0.75 mg two-dose regimen. The objectives of this study were:

- to compare the efficacy of a single dose of mifepristone 10 mg with levonorgestrel 0.75 mg administered in two doses 12 hours apart and with a single dose of levonorgestrel 1.5 mg.
- to assess whether the same effectiveness can be achieved by extending the postcoital treatment up to 120 hours.

The levonorgestrel tablets for this WHO trial were manufactured by Gedeon Richter, the manufacturer of the levonorgestrel product for this current NDA. The tablets used in this study were Postinor02 with gelatin. In a March 2, 2006 submission the sponsor confirmed that the

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Levonorgestrel is primarily protein bound, approximately 50% to albumin and 47.5% to sex hormone binding globulin. Following a single dose of levonorgestrel 1.5 mg, the maximum drug plasma concentration of 19.1 ng/mL was reached at 1.67 hours (range 1 – 4 hours). The elimination half-life is  $27.49 \pm 5.59$  hours. The drug is not extensively metabolized by the liver. The primary metabolites account for less than 10% of the parent plasma levels. Urinary metabolites have also been identified. Levonorgestrel and its metabolites are primarily excreted in the urine, with a smaller amount recoverable in the feces.

This product is not intended for use in the geriatric population, nor in the premenarcheal populations. Pharmacokinetic data are not available for these groups.

#### **6. Clinical Microbiology**

There were no clinical microbiology data submitted with this application because of lack of relevancy.

## **7. Clinical/Statistical - Efficacy**

### **General Discussion:**

Refer to the reviews by Dr. Daniel Davis (November 22, 2006) and Lisa Soule (November 22, 2006) for the details of the study designs. In his clinical review, Dr. Daniel Davis pointed out that a dose of levonorgestrel 1.5 mg was approved in over 100 countries for emergency contraception and that levonorgestrel had seen widespread use both as a two-dose regimen and, in 27 countries, as a single dose regimen. In 2006, the single dose regimen was available directly from a pharmacist in eight countries and was available OTC in Sweden and the Netherlands.

The Division of Reproductive and Urologic Products held teleconferences with Duramed in November, 2005 and in January, 2006 to discuss the requirements for this NDA submission. As stated in Dr. Scott Monroe's November 22, 2006 Division Director memorandum, DRUP agreed to accept one adequate and well-controlled study as adequate proof of safety and effectiveness because one levonorgestrel 1.5 mg tablet is the same total dose as one therapeutic treatment with Plan B®, two levonorgestrel 0.75 mg tablets taken 12 hours apart. In accordance with this, the sponsor submitted WHO/HRP 97902 (see the clinical pharmacology section above). As supportive evidence of safety and efficacy, the sponsor also submitted a literature publication<sup>1</sup> from a randomized, double-blind, comparative trial in Nigeria of 1118 evaluable women requesting emergency contraception within 72 hours after unprotected intercourse. Dr. Davis comments that the main difference between the two studies reviewed was that women in the WHO Study could enroll up to 120 hours following unprotected intercourse, but in the Nigerian study they could enroll up to 72 hours following unprotected intercourse. Otherwise, in both studies women were enrolled on the basis of regular menstrual cycles, unprotected intercourse, and agreement to refrain from further intercourse until their next menses had occurred. The primary efficacy outcome measure for this NDA was prevention of pregnancy using the prevented fraction (proportion of expected pregnancies prevented by the treatment) as the primary efficacy variable; this is considered to be an excellent measure of efficacy since it accounts for the estimated probability of conception on the day of unprotected sex. Refer to Dr. Davis' review for details.

The FDA analysis of the WHO study only considered the two levonorgestrel arms, because the NDA did not seek approval of mifepristone for emergency contraception and no comparative claims relative for the use of mifepristone for emergency contraception are made in the NDA.

### **WHO Study Results:**

These data are presented in detail in tabular form in the November 2006 reviews by Dr. Davis, Dr. Soule, and Dr. Monroe.

### **Primary and Secondary Efficacy Analyses:**

Women aged 14 – 52 (mean age 27 years) enrolled in the study; there were no age limitations placed on enrollment. One thousand three hundred seventy-nine women were randomized to

<sup>1</sup> 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.

receive the levonorgestrel 1.5 mg and 1377 were randomized to receive the levonorgestrel 0.75 mg (two doses). The results of the WHO study showed that the two levonorgestrel emergency contraception regimens are highly effective in preventing pregnancy. The data assessing the ITT population subjects who enrolled within 72 hours of unprotected intercourse demonstrated that the single dose 1.5 mg levonorgestrel regimen and the two dose 0.75 regimens were similarly effective, 83.95% (CI 73.94 – 90.83) of expected pregnancies prevented compared to 79% (CI 67.44 – 87.12) respectively; the difference in expected pregnancies prevented was not statistically significant, although it was numerically higher for the single dose product. The expected pregnancy rate of 8% with no contraceptive use was reduced to approximately 1% with Plan B® One-Step.

A secondary efficacy analysis measure was the relative risk (RR) of pregnancy in women using the single and two-dose regimens. The crude RR was 0.79, with a confidence interval that spanned 1, indicating no significant difference. The adjusted RR of pregnancy, which controlled for the number of expected pregnancies in each group, was similar 0.76, again with a confidence interval spanning 1.

#### Timing of Treatment:

A trend toward lower efficacy with a longer delay in taking the levonorgestrel after unprotected intercourse was shown for the ITT population when considering pregnancy rates for treatment within 0 to 72 hours compared with 73 to 120 hours. This was the case for both the single dose and the two-dose regimens. A statistically significant difference was found in efficacy between women starting the treatment within 96 hours (1.48% pregnancy rate) and after 96 hours (4.8% pregnancy rate) of unprotected intercourse. The data also showed that pregnancy rates were lower if further acts of protected and unprotected intercourse did not occur following treatment. Treatment is effective for women of all reproductive ages, < 35 years and > 35 years. (These are the age cutoffs by which these data were analyzed.)

In her September 26, 2006 review the statistician, Dr. Sonia Castillo, stated that the sponsor had provided an adequate study that resulted in a prevented fraction of 81.9% (95% C.I. 72.0% – 88.9%) for levonorgestrel 1.5 mg for use as an emergency contraceptive. As Dr. Monroe points out in his review, the values Dr. Castillo cited were based upon the ITT population for women who took a single dose of levonorgestrel 1.5 mg up to 120 hours post unprotected coitus. Dr. Castillo provided an addendum to her statistical review, dated November 21, 2006, verifying the sponsor's efficacy analyses demonstrating a prevented fraction of 83.95% (95% C.I. 73.94 – 90.83) in the ITT population subgroup of women presenting for treatment within 72 hours of intercourse.

#### Chinese Population:

On pages 21 – 22 of his review, Dr. Davis presents the analysis of the WHO study efficacy data comparing Chinese and non-Chinese populations. Fifty-four percent of the enrollees were Chinese and 46% were not. In the Chinese population the percentage of pregnancies prevented was numerically less than in the non-Chinese population. However, the WHO Study 97902 did not demonstrate a statistically significant decrease in contraceptive efficacy for these two populations comparing the two dosing regimens when used up to 120 hours or when used in the up to 72 hours after unprotected sex subset. The prescription label for Plan B®, reflecting

data in the original Plan B® NDA, states that clinical trials demonstrated a higher pregnancy rate in the Chinese population with both Plan B® and the Yuzpe emergency contraception regimens and the reason for this is unknown. Dr. Davis agrees with the sponsor that the labeling for Plan B® One-Step should have the same information in the prescription Package Insert.

In her review, Dr. Soule comments that if the fecundity of Chinese women is higher than the population on which the conception day probabilities were derived, the expected numbers of pregnancies might be underestimated, leading to an underestimate of prevented fraction, and therefore of the efficacy of levonorgestrel as an emergency contraceptive in Chinese women.

#### **DSI Audits:**

The DRUP reviewers found the data quality and integrity acceptable. Original datasets were submitted as requested. Dr. Davis comments that the 15 sites in 10 different countries are part of the United Nation's WHO/HRP network and that 14 of the 15 sites have been involved with several WHO sponsored reproductive studies over many years. DRUP did not request inspections for this study because:

- these centers had been routinely monitored through this and previous WHO trials
- the original case report forms were submitted as part of the NDA
- of the large size of this blinded and randomized trial that essentially was studying a new regimen for a single use of a proven product (Plan B®) for emergency contraception

#### **Nigerian Trial Results:**

The original datasets and case report forms were not available for the analysis of this large, blinded, comparative study. Six hundred women took the single dose 1.5 mg levonorgestrel and 560 women took the two-dose 0.75 mg levonorgestrel 12 hours apart. The mean age of the study participants was 27 years. Of the 1118 evaluable patients eleven pregnancies were reported, four in the single dose group and seven in the two-dose group. The crude relative risk of pregnancies was similar in the two groups; for the single dose compared to the two-dose regimen, the crude RR = 0.71 (95% CI 0.32-1.55;  $p > 0.05$ ). However, according to the publication, the estimated 86.8% pregnancy prevented fraction, also called the effectiveness rate, in the two-dose levonorgestrel group was significantly lower than the prevented fraction of 93.0% for the single dose levonorgestrel group ( $p < 0.05$ ). The pregnancy rates increased as the delay in starting treatment after unprotected intercourse increased and if further acts of unprotected intercourse took place after treatment. Dr. Davis concluded from this study that (a) single dose levonorgestrel is at least as effective as the two dose regimen, (b) the earlier either product is given, the greater the efficacy, and (c) pregnancy rates increase if further acts of intercourse occur following treatment and prior to the next menstrual period.

With regard to the overall assessment of efficacy, the DRUP concluded the following should appear in labeling:

- Women should take Plan B® One-Step as soon as possible after unprotected intercourse and within 72 hours after the event.



- Further acts of unprotected intercourse before the onset of the next menstrual period should be strongly discouraged, as this will decrease the effectiveness of the treatment and increase the likelihood of an unplanned pregnancy.
- Effectiveness in Chinese women may be slightly, but not statistically significantly, lower compared to non-Chinese women. After communicating with Drs. Davis, Soule and Monroe on June 26, 2009, I learned that they feel that this information should appear in the prescription Package Insert, but that it is not useful to put it in the OTC labeling.

In Dr. Christina Chang's July 7, 2009 review she comments, "*Because it is unlikely that the information about possible racial differences in efficacy of unknown clinical significance would have any utility to the consumer, the information is unnecessary on the OTC label.*" The information on Chinese women in the prescription labeling for Plan B® was not included in the OTC labeling for Plan B®. Considering:

- the absence of a statistically significant difference in efficacy between this and other populations
- Dr. Soule's observation as stated above on fecundity
- that the OTC consumer cannot act in a particular way to maximize the effect of emergency contraception based upon this information

I think that to add this information to the Plan B® One-Step OTC label may offer no value and may actually distract the eye of the consumer from more important and useful messages on the OTC label.

#### Efficacy Summary:

In summary, I agree with the reviewers in DRUP that the prevented fraction of expected pregnancies with Plan B® One-Step is acceptable and that this single dose regimen is as effective in preventing pregnancies as the two-dose Plan B® regimen.

### **8. Safety**

#### Clinical Trials:

The safety population from the WHO study included all women who took at least one dose of study medication. Since all women took the first dose of study medication under supervision, 1,379 women were in the single dose safety analysis and 1,377 were included in the two-dose group. Study participants kept a diary of adverse events. See the review by Dr. Davis for the details about adverse event recording. The Nigerian study provided a study population of 1062 women exposed to study drug with sufficient information to assess adverse events and timing of next menses. Neither study reported whether women who dropped out or were lost to follow-up (1.5%) had experienced adverse events.

There were no deaths in the WHO study or in the Nigerian Study. Three serious adverse events (SAEs) were reported in the WHO study but none in the Nigerian Trial. The WHO SAEs were as follows:

- Single dose treatment: one ruptured corpus luteum cyst eight days post treatment, one acute appendicitis. Neither of these cases was thought by the investigator to be related to study drug.
- Two-dose treatment: one ectopic pregnancy

**Ectopic pregnancy:**

In March, 2004, Dr. Davis conducted a review of the safety of Plan B®, including a thorough evaluation of serious adverse events and ectopic pregnancies. The data from that review demonstrated that Plan B® was safe. Dr. Davis noted that up to 10% of pregnancies reported in clinical studies of *routine use* of progestin-only contraceptives are ectopic. Therefore, a warning about ectopic pregnancies appears in the Plan B® labeling and will appear in the Plan B® One-Step labeling. However, the data from the WHO and Nigerian Trials are consistent with the safety of levonorgestrel as an emergency contraceptive regarding ectopic pregnancy. There were 44 pregnancies in the WHO study and 1 ectopic; of the eleven pregnancies in the Nigerian Trial, none were ectopic. Dr. Davis comments that taking these data together, among 55 pregnancies, there was 1 ectopic, a 1.8% incidence and that this is consistent with the expected 1-2% of all pregnancies which are expected to be ectopic.

**Timing of Menses:**

Levonorgestrel for emergency contraception can result in an alteration in the timing of menses. The adverse event profile for the women in the Nigerian Study was similar to the WHO data, although, as Dr. Soule comments, it appears that the impact of the single dose product on menstrual cycle latency and severity may have been more pronounced in the Nigerian study based upon the delay of menses and rate of heavy menses reported in that population.

**Most Common Adverse Events:**

Other adverse events reported in the WHO study that may have been related to the study drug were not unexpected based upon what we know about levonorgestrel. The incidence of these adverse events did not differ significantly between the levonorgestrel 1.5 mg and levonorgestrel 0.75 dosing regimens. Refer to Table 15, page 30 of Dr. Davis' review. The most common adverse effect was heavier menstrual bleeding (31%) followed by nausea (14%), lower abdominal pain (13%), fatigue (13%) headache (10%), dizziness (10%), breast tenderness (8%), and delay of menses > 7 days (5%). In the Nigerian Trial the most common adverse events were nausea, lower abdominal pain, and dizziness.

**Safety Update, 2006:**

In 2006, the sponsor submitted a postmarketing safety update covering the time period January 1, 2006 to June 30, 2006 for both the two dose and the single dose levonorgestrel products. Dr. Soule noted that over the reporting period, the sponsor estimated that there were over \_\_\_\_\_ uses of levonorgestrel as an emergency contraceptive worldwide. More than \_\_\_\_\_ uses occurred in the 60 countries where the two-dose regimen was marketed and \_\_\_\_\_ uses occurred in the 21 countries where the single dose regimen was marketed. Of all of these uses, 105 adverse event reports were received and among these 20 cases of pregnancy were reported and one case of pruritus. The remaining reports were of nonserious, listed, unconfirmed and follow-up adverse events. These data did not differentiate between adverse events stemming from the two regimens, but the clinical trial data suggest that the safety profiles of the two dosing regimens are similar.

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Safety Update for Complete Response Submission, 2009:

In July 2009, Dr. Davis and Dr. Soule reviewed the Safety Update provided by Duramed on June 9, 2009 as part of the Complete Response. These data consisted of recent safety reports covering the U.S. marketed Plan B and also European data on both single dose and two dose levonorgestrel emergency contraceptive products. The data reviewed for the safety update included:

- Summary pages from Duramed for July 2007 – July 2008 Periodic Report for Plan B®: During this Reporting Period, Duramed estimated that approximately \_\_\_\_\_ U.S. women were exposed to Plan B®. During this period there also were 9,029 individual case reports describing 15,432 adverse events. According to Dr. Davis' review, only seven of these adverse events, involving five individuals, were listed as both serious and medically confirmed. These seven reports included two reports of ectopic pregnancy and one report each of spontaneous abortion, missed abortion, blood in urine, pancreatitis, and cytomegalovirus infection (CMV). The adverse event of "blood in urine" was reported in association with one of the cases of ectopic pregnancy, where vaginal bleeding can commonly contaminate a urine specimen. The adverse event of "pancreatitis" was considered secondary to the CMV infection (both events being reported in a single case). Plan B® was not considered in the report to be related to either of the adverse events. Of the ten most commonly reported adverse events during the Reporting Period, eight were previously described in labeling. Dysmenorrhea and pelvic pain were the two adverse events not presently included in product labeling

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The sponsor is monitoring the following adverse events to see if an association is ultimately determinable: hypersensitivity, loss of consciousness, syncope, dyspnea, and erythema nodosum. The cases of these adverse events in the sponsor's database were medically unconfirmed. There was a single case of erythema nodosum, which has not been reported with Plan B® previously. See Dr. Davis' review for the details.

The reviewers did not see any new significant safety signals in these Duramed data, but did recommend that the prescription labeling list "dysmenorrhea" and "pelvic pain" as adverse events. I agree with Drs. Chang and Furlong (see their July 7, 2009 review) that the OTC labeling covers this concern with the "lower stomach (abdominal) pain" warning.

- Gedeon Richter periodic safety update report covering from July 2008 – December 2008 with data for both the single and two-dose products with over \_\_\_\_\_ uses of their products worldwide: Dr. Davis and Soule did not see new safety signals in these data. The three most commonly reported adverse events were spontaneous abortion, irregular bleeding, and delayed menstruation. In Dr. Soule's July 9, 2009 Cross-Discipline Team Leader Review she comments that irregular bleeding and delayed menstruation are known adverse effects of levonorgestrel emergency contraception. She also comments that given that levonorgestrel does not prevent 100% of pregnancies following unprotected intercourse and given the known rate of spontaneous abortions (up to about 20% or even 25% of all conceptions), the reports of spontaneous abortion are not unexpected and do not constitute a safety signal.

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Also reviewed were:

- Three AERS updates by FDA's Office of Surveillance and Epidemiology Division of Pharmacovigilance II for Plan B® through May, 2009 (See below): These reports did not raise new safety concerns that would generate the need for new warnings at this time.
- OTC and pharmacy availability provided by the Applicant: These data demonstrate that levonorgestrel was available without a prescription from a pharmacist in 44 countries by March 2009. It was available OTC without any age restriction in 5 countries: Canada (as of June 2009), Norway, Sweden, Holland, and India and in the U.S. for those ages 18 years and older. In China emergency contraception is to be obtained from a pharmacist, but in reality women are able to buy the medicine OTC. In May 2009, Spain announced that emergency contraception would be available OTC in pharmacies within three months
- Scientific Literature update from 2006 to the present: No new safety signals emerged from the literature review conducted by Dr. Davis. He concluded that the overwhelming evidence from the literature is that levonorgestrel is safe, efficacious, and well-tolerated.

#### FDA's Office of Surveillance and Epidemiology

In September 2006, FDA's Office of Surveillance and Epidemiology reviewed all of the adverse event reports naming Plan B® or levonorgestrel for emergency contraception found in the FDA's Adverse Event Reporting System (AERS) database since the approval of Plan B® as a prescription product in 1999. Those data did not raise new concerns about the safety of levonorgestrel as an emergency contraceptive. In a 2008 review of the AERS data, OSE suggested that DRUP consider requesting the sponsor to conduct a comprehensive review of syncope and loss of consciousness because there was a suggestion of a possible temporal relationship in the small case series. DRUP did not concur with this recommendation because of the small number of cases and lack of adequate documentation. DRUP did agree, though, that the Division of Adverse Events Analysis should continue to monitor the AERS reports and the sponsor should do the same.

Since approval of Plan B® in 1999, only two fatalities have been reported in U.S. patients. One of cases was the death of a 21-year-old woman with extensive concomitant drug use, for whom OSE felt that the death was unlikely to be related to the use of Plan B®. The other case was a death of unknown cause three days after birth in a premature infant born at 5 months gestation to a 31-year-old woman. According to the OSE review, she took her first dose of Plan B® on an unknown date in December 2005 and became pregnant afterwards. There is no more information on this case.

In another review dated June 2009, the Division of Pharmacovigilance from the Office of Surveillance and Epidemiology completed an update to a comprehensive safety review of Plan B® completed in April 2008. Also included in this review was a summary of all adverse event reports in patients < 18 years old received since the 1999 market approval. There were only 13 cases identified in this age group and no serious, unlabeled events were seen. In his July 2009 safety update review, Dr. Davis comments that we know via data submitted by the sponsor that there are about \_\_\_\_\_ prescriptions for Plan B® filled in this population annually. The most

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recent review of the AERS database did not contain any new fatalities associated with Plan B®.

Four case reports involved dizziness/fainting (one case was of a woman after watching her boyfriend feed a mouse to a snake). These symptoms will continue to be monitored by the sponsor and by the OSE, as well as syncope and loss of consciousness. Overall, the OSE reviews did not identify safety signals for Plan B® and the OSE review did not recommend adding new labeling warnings. I agree.

Safety Data Summary:

Levonorgestrel is sold as an emergency contraceptive in many countries and, to the best of our knowledge, as of the date of this review has never been withdrawn or suspended from marketing for safety reasons. The primary and secondary reviewers concluded that that levonorgestrel 1.5 mg is safe and well-tolerated as an emergency contraceptive. The total dose for a treatment regimen for Plan B® One-Step and Plan B® are the same and the safety profiles do not suggest differences of clinical concern. I agree with the reviewers and with Dr. Monroe that the data support a favorable benefit/risk profile for Plan B® One-Step.

Consumer Considerations:

For the Plan B® NDA 21-045/S-011, a Label Comprehension Study and an Actual Use Study were conducted by the sponsor. The data from these studies strongly indicated that the study participants understood the labeling and could use the product properly, without the intervention of a healthcare provider. These data supported the OTC switch of Plan B®. The labeling for Plan B® One-Step is very similar to that of Plan B®, the major exception being that the new product is a one dose treatment, instead of two-dose treatment timed 12 hours apart. This means that it is even easier to comply with the directions for use for the new product. For the following reasons, I am not concerned that women will mistakenly take two of tablets instead of one:

- the directions are simple and clear,
- one tablet will be in the package, not two,
- even the product name implies that there is only one thing to do

In my view, the label comprehension and actual use data from NDA 21-045/S-011, Plan B®, support that Plan B® One-Step will be used appropriately by OTC consumers.

Modified CARE<sup>SM</sup> Program:

Duramed has volunteered to conduct a modified CARE<sup>SM</sup> Program for Plan B® One-Step.

The program outlines the following elements:

- Labeling/Packaging/Informational toll free number (to provide essential information to consumers in an accessible, easy to understand format. The Plan B® One-Step packaging is designed to meet both prescription and OTC requirements.)
- Education (to provide information intended to educate physicians, pharmacists, pharmacy staff, nurse practitioners, and patients. Educational initiatives will focus on clearly instructing all audiences on the new dosing regimen of a single tablet, and the new lower age requirement that women younger than age 17 obtain a prescription for Plan B® One-Step.)

- **Distribution** (to ensure that Plan B® One-Step will be available only to licensed drug wholesalers, retail operations with pharmacy services and clinics with licensed healthcare practitioners, and to successfully facilitate the Plan B® One-Step prescription-only age requirement. These settings will also provide easy access by the consumer to a pharmacist or other healthcare professional should questions arise.)
- **Monitoring** (to evaluate the effectiveness of the program by determining if the age restriction is understood by all audiences and is properly being adhered to.)

None of the reviewers in DRUP or in DNCE consider this to be a necessary program for safety, efficacy reasons or compliance reasons. The product is safe and effective for all post-menarcheal females at risk of getting pregnant and data from the CARE<sup>SM</sup> program for Plan B® demonstrate that pharmacists are careful about providing the OTC product only to those who are eligible based upon age.

#### **9. Advisory Committee Meeting**

On December 16, 2003, an Advisory Committee meeting was convened for NDA 21-045/S-011 to discuss the OTC switch of Plan B®. The committee voted overwhelmingly in favor of a complete OTC switch with no age restriction for Plan B®. The committee voted (27 to 1) that the Actual Use Study data could be generalized to the overall population of potential OTC users of Plan B®. They recommended that Plan B® be switched from prescription to OTC (23 to 4 with one member having left before voting). All of the medical reviewers from DRUP, among them Drs. Davis, Griebel, and Monroe, the Deputy Director of the Division of OTC drug products, Dr. Rosebraugh, the ODE V and ODE III Directors Drs. Bull and Beitz, the Director of the Office of New Drugs, Dr. Jenkins, and I agreed with the committee that the data available on this product, including the consumer studies supported a complete switch. No controversial data emerged from NDA 21-998 to generate the need for another advisory committee meeting and for this reason, none was held.

#### **10. Pediatrics**

The PeRC PREA Subcommittee met on April 9, 2009 and granted a partial waiver for pre-menarcheal patients because pre-menarcheal patients are not at risk of becoming pregnant and the use of this product before menarche is not indicated. The Division also noted that the pediatric study requirement for post-menarcheal pediatric patients has been met by the extrapolation of adult data.

#### **11. Other Relevant Regulatory Issues**

**Application Integrity Policy (AIP):** This sponsor is not on the AIP list.

**Exclusivity/patent issues:** The applicant declared that there are no patents with respect to which a claim of infringement could be reasonably asserted. Thus a patent certification is not applicable. There are no financial disclosure concerns.

#### **12. Labeling**

##### **Trade Name:**

The Division of Medication Error, Prevention, and Analysis accepted the name Plan B® One-Step for this product. I agree that this name is acceptable.

OTC Labeling:

Medical Content:

Here I will highlight the important considerations regarding the informational content of the OTC labeling. Dr. Scott Monroe will consider the prescription labeling in his review.

In her review, Dr. Christina Chang describes a Label Comprehension Study in teenagers by Raymond et al, conducted by independent investigators on Plan B® One-Step and published in 2009.<sup>2</sup> Since Duramed supplied only the prototype labeling without sponsoring the study, they did not have access to raw data from the study. One hundred seventy-one adolescents aged 15 to 17 years enrolled in the study. A high proportion of this group understood five of the six key concepts tested (94% to 98%). Eighty-six percent of adolescents understood the key concept having to do with optimal timing for taking Plan B® One-Step (Levonorgestrel 1.5 should be taken as soon as possible after sex), but this was bolstered by the fact that 98% correctly understood the 72-hour time frame (Levonorgestrel 1.5 should be taken within 72 hours after sex). The authors thought this discrepancy may possibly be due to the adolescents' tendency toward a more concrete cognitive pattern. Therefore, the authors suggested that combining the two instructions pertinent to timing of administration such as: "Levonorgestrel 1.5 should be taken as soon as possible after unprotected sex but not more than 72 hours later," may be helpful to the more literal-minded adolescents. Dr. Chang comments that the sponsor appears to have incorporated this recommendation by stating under *Directions* in the Drug Facts:

"Take tablet as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take it the better it will work."

The currently approved Plan B® label directs the consumer to call a healthcare professional if vomiting occurs within one hour of taking either dose of the medication. The sponsor proposed the following instruction should vomiting occur after taking Plan B® One-Step:

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The sponsor also proposed the 2-hour limit for Plan B®. Since Plan B® is a two-dose product there is the concern that women will not know when to take the second dose of medication if the first dose is repeated due to vomiting.

The proposed 2-hour time frame is based upon the  $T_{max}$  of levonorgestrel 1.5 mg and 0.75 mg. This pharmacokinetic information led the WHO expert Working Group to consider two hours sufficient for hormone absorption with no further action necessary if a woman vomits after this time. However, Duramed acknowledged that the company has not conducted studies to determine the appropriate management should vomiting occur after taking Plan B® or Plan B® One-Step. Drs. Christina Chang and Lesley-Anne Furlong (who are both obstetrician/gynecologists) note that, in the practice of medicine, healthcare provider responses to vomiting following ingesting the emergency contraceptive vary since optimal management

<sup>2</sup>Raymond EG, L'Engle KL, Tolley EE, Ricciotti N, Arnold MV et al. Comprehension of a prototype emergency contraception package label by female adolescents. *Contraception* 2009; 79: 199-205.

in this situation is unresolved. Some recommend repeating the dose with or without an antiemetic and others do not. Drs. Chang and Furlong also informed me that other management options may include another post-coital contraceptive such as an intrauterine device.

Given that both Plan B® and Plan B® One-Step will be marketed simultaneously, Drs. Chang and Furlong recommend that it would be prudent to have consistent language for both regimens to minimize confusion. I concur. The sponsor was asked to use the following language in the labeling for these products:

For Plan B® One-Step

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

For Plan B®

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

I agree with the rationale presented by Drs. Chang and Furlong for including “vomiting” in the OTC Drug Facts label Warnings section and not including “diarrhea.” Refer to their review.

After multiple labeling revisions by the sponsor, Arlene Solbeck and Marina Chang finalized their review of the labeling on July 9, 2009 and found the three labeling components (retail carton, clinic carton, and consumer information leaflet) acceptable for approval. They reminded the sponsor to delete the statement “NEW! Now only ONE dose” six months after introduction into the marketplace.

### **13. Decision/Action/Risk Benefit Assessment**

#### **Conclusion:**

Plan B® has been available OTC for women 18 years of age and older since 2006. However, the Agency position since 2005 was that Plan B® was safe and effective for OTC use for women ages 17 and over. It was an unsubstantiated concern about enforceability of age distinction that led to the OTC marketing to women at least 18 years of age.

Duramed has sought OTC approval for Plan B® One-Step for women ages 17 years of age and older and prescription approval for those less than age 17. I agree with the entire medical review team from both DRUP and DNCE that the sponsor has demonstrated that levonorgestrel 1.5 mg is a safe and effective emergency contraceptive for females of reproductive age. The product is to be taken as a single tablet as soon as possible within 72 hours of unprotected sexual intercourse to reduce the chance of pregnancy.

The Code of Federal Regulations 21 CFR 310.200 states:

*Any drug limited to prescription use under section 503(b)(1)(B) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures*



*necessary to its use, and he find that the drug is safe and effective for use in self-medication as directed in proposed labeling.*

Therefore, for a drug to be OTC, the labeling must convey all of the information needed to use the product safely and effectively in the absence of a healthcare practitioner. The label comprehension and actual use data (whether on the single dose or two-dose levonorgestrel emergency contraceptive regimens) confirm that women 17 years of age and older know what the emergency contraceptive is for and how to take it, based upon the product labeling. Healthcare provider involvement is not necessary for proper use by this target OTC population.

By virtue of the data submitted by Duramed in NDA 21-998, Plan B® One-Step meets the requirements of the codified statute for an OTC drug (21 CFR 310.200) for the targeted OTC population of women. If the sponsor wishes to pursue OTC marketing for the population of females less than 17 years of age, they will need to submit the appropriate supportive information in an efficacy supplement.

Three months after having sent the April 21, 2009 letter to Duramed, I remain unaware of data that support a distinction between ages 17 and 18 in terms of enforceability of an age restriction. Furthermore, we know that pharmacists diligently check the age of Plan B® purchasers and can distinguish among the consumers who are eligible to purchase the OTC product and those who are not. The science (as consistent with CDER's position since 2005) and the data on pharmacist behavior do not support continuing to deny 17-year-olds, who could benefit from Plan B® or now from Plan B® One-Step, OTC access to the medication.

It is important to note the Office of the Chief Counsel (OCC) at FDA has consistently advised DNCE, \_\_\_\_\_

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\_\_\_\_\_ This issue has been the topic of public discussions at Advisory Committee meetings during committee deliberations over several OTC switch applications before and subsequent to the Plan B® approval in 2006. It has also been the subject of discussion at many proprietary meetings that DNCE has had with industry regarding product development. As of the time of this review, I am unaware of any change in interpretation of the law that would modify the advice that we have consistently received from OCC. Therefore, as with all other OTC products, the label and labeling for OTC Plan B® One-Step must accomplish the necessary education for proper product use on its own. With that history, I will now discuss the CARE<sup>SM</sup> Program.

**CARE<sup>SM</sup> Program:**

A generic version of Plan B® was approved last month without the requirement that the sponsor conduct a CARE<sup>SM</sup> Program; this was a prescription product for women age 18 years and younger. Consistent with the views of the medical reviewers in DRUP and DNCE, in my view, the CARE<sup>SM</sup> program is not needed to support the "OTCness" of Plan B® or Plan B® One-Step going forward.

The Plan B® One-Step product Drug Facts label and labeling (Consumer Information Leaflet) are sufficient to provide OTC consumers with the information that they need to use the product properly. Reliance upon the product label and labeling to result in appropriate use is consistent with the tenet that the Agency has applied in the past and continues to apply when determining whether or not a product can be over-the-counter. It is an approach consistent with the regulations.

However, Duramed has volunteered, as they did with Plan B®, (refer to Dr. von Eschenbach's August 23, 2006 memorandum) to conduct a modified CARE<sup>SM</sup> Program for Plan B® One-Step. Considering each of the core elements of this program, two of them (labeling and distribution) describe what constitute lawful marketing of Plan B® One-Step. Whether written down in a CARE<sup>SM</sup> program or not, compliance with these elements is mandated. I have no objection to the other elements as proposed (e.g., educational programs for healthcare professionals and consumers, plan to monitor trends in the use of emergency contraception, continuing to conduct the Point-of-Purchase Monitoring Program).

Recommendations:

Regulatory action: NDA 21-998, Plan B® One-Step, should be approved OTC for women 17 years of age and older with the agreed upon OTC label and Consumer Information Leaflet labeling as negotiated between DNCE and Duramed. DRUP has negotiated the labeling with Duramed for the prescription product.

Because of the single packaging configuration for dual marketing status of the product, the sponsor cannot legally market Plan B® One-Step to convenience stores and gas stations. The product can only be distributed to licensed pharmacies or other licensed healthcare clinics.

Duramed can voluntarily conduct the modified CARE<sup>SM</sup> Program as described and proposed. However, they should let us know if they plan to make changes to the program in the future so, for example, we can be sure that accuracy is preserved and that the changes are not promotional in nature.

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Andrea Segal  
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MEDICAL OFFICER