

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-998**

**MEDICAL REVIEW(S)**

## **CLINICAL REVIEW**

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

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

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

It is important to note that the original recommendation (2004) from DRUP (Division of Reproductive and Urologic Products) and the Office of Drug Evaluation III (ODE III) regarding a switch from prescription to OTC status for the two-dose levonorgestrel emergency contraceptive product, Plan B, was that full OTC availability was acceptable, and that there did not need to be any age restriction. Furthermore, the joint Advisory Committees for Reproductive Health Drugs and Nonprescription Drugs met on December 16, 2003 to consider the Rx/OTC switch application for Plan B, and recommended by a vote of 23 to 4 that Plan B was sufficiently safe to be distributed over the counter without any age or distribution restrictions and without any further studies before approval. I continue to believe, based on all the clinical trial results, available medical literature, and postmarketing data, that both Plan B and Plan B One-Step could be safely used by women of all ages in the absence of a "learned intermediary;" i.e., the product is appropriate for OTC marketing to all women of childbearing age. Therefore, approving Plan B One-Step as an OTC product for women age 17 and above is consistent with the distribution plan that has been recommended by DRUP, ODE 3, and a joint Advisory Committee for levonorgestrel emergency contraception ever since the initial request for an Rx/OTC switch for Plan B.

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

### **1.2 Risk Benefit Assessment**

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

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

None are recommended.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

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

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

## **2 Introduction and Regulatory Background**

In July 1999, levonorgestrel 1.5 mg (divided into two 0.75 mg tablets taken 12 hours apart), was approved for emergency contraception in the U.S. under NDA 21-045 and has been used extensively since then, marketed as Plan B. The Applicant submitted Supplement 011 to NDA 21-045 on April 22, 2003 for a switch from prescription status to OTC status for Plan B. In December 2003, a joint Advisory Committee (Reproductive Health Drugs and Nonprescription Drugs) meeting was held to discuss the switch from prescription status to OTC status. The Committee recommended by a vote of 23 to 4 that Plan B was sufficiently safe to be distributed over-the-counter without any age or distribution restrictions and without any further studies before approval. The original PDUFA date was February 22, 2004 and a 3-month extension was granted, extending the date to May 22, 2004.

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

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

On July 21, 2004, the Applicant submitted a Complete Response to the Not-Approvable letter and requested that Plan B remain available by prescription only for women under age 16 and be switched to OTC status for women age 16 and older. On August 26, 2005, the Commissioner of the FDA, Dr. Lester Crawford, notified the Applicant that CDER had concluded that submitted data were sufficient to support use of Plan B as an OTC product only for women aged 17 and older. However, unresolved issues precluded a decision on the approvability of the submission:

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

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

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

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

women ages 18 and over. Therefore, before this application may be approved, you will need to submit revised labeling that meets the requirements of marketing of levonorgestrel tablets, 1.5 mg, as a prescription product for women 17 years of age and younger, and as a nonprescription product for women 18 years of age and older. You will also need to submit your plan regarding distribution of both the Rx and OTC versions of your product.

Further comments on labeling are deferred until the above deficiency is addressed.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level."

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

Subsequently, on March 23, 2009, a final decision was reached in the US District Federal Court (NY) case *Tummino v. von Eschenbach et al.* concerning the FDA's decision process and restriction to age 18 and older for the OTC switch for Plan B. The plaintiffs' claim was that the FDA's decisions "were arbitrary and capricious because they were not the result of reasoned and good faith agency decision-making." The court ordered the FDA to act within 30 days to extend the OTC access to 17 year-olds. On April 22, 2009, a press release by the FDA stated that "FDA notified the manufacturer of Plan B informing the company that it may, upon submission and approval of an appropriate application, market Plan B without a prescription to women 17 years of age and older." At the same time, the Director of DNCE sent a letter to Duramed outlining what would be required if Duramed decided to pursue OTC marketing of Plan B for women age 17 and older.

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

## **2.1 Product Information**

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

## **2.4 Important Safety Issues with Consideration to Related Drugs**

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

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

See detailed discussion in Section 2 above.

### **Labeling:**

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

### **Safety Update:**

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

## **2.6 Other Relevant Background Information**

Refer to section 2.0 for relevant background information.

## **3 Ethics and Good Clinical Practices**

See the original NDA reviews. No issues were noted.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

There are none.

## **5 Sources of Clinical Data**

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

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

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

## 6 Review of Efficacy

### *Efficacy Summary*

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

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

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

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

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

Concerning efficacy it is important to emphasize the following:

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

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

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

### **6.1 Indication**

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

## **7 Review of Safety**

### **7.1 Methods**

#### ***Safety Summary (original NDA review)***

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

#### **Safety Review (new materials and consults)**

The following new information was reviewed for this safety update:

1. AERS update by DAEA (Division of Adverse Event Analysis)<sup>1</sup> for Plan B through 3-08

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

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

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**AERS Updates:**

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

“A comprehensive review of Plan B® (levonorgestrel tablets 0.75 mg) was undertaken upon receipt of the sponsor’s U.S. Periodic Report and approximately a year has elapsed since the dually labeled product for Rx or OTC use was released to pharmacies. This comprehensive review included a review of potentially significant data mining scores for Plan B and searches in the AERS database for the most commonly reported preferred terms and reports of congenital anomalies, fatalities, and thromboembolic events for Plan B. This comprehensive review of Plan B data mining scores and reports in the AERS database did not identify any adverse events that should be considered for inclusion in the labeling at this time. For the reports of syncope and loss of consciousness reviewed herein, there was a suggestion of a possible temporal relationship with Plan B administration in this small case series. The division should consider requesting that the sponsor conduct a comprehensive review of syncope and loss of consciousness.

The sponsor stated in the U.S. Periodic Report for the period of 01 July 2006 through 30 June 2007 that they will conduct an assessment of all reports of pelvic pain and dysmenorrhea, which were primarily non-serious reports. The DAEA (Division of Adverse Event Analysis) will continue to monitor this product for any new potential safety signals or events of concern (i.e. thromboembolic events).”

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

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

The Executive Summary from the recent DPV 2009 review follows:

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

An AERS search for all domestic adverse event reports for Plan B in patients less than 18 years of age received since 1999 market approval retrieved 13 domestic cases [age range 15-17] for analysis. An AERS search for all domestic adverse event reports for Plan B with no age restriction received since March 12, 2008 (data lock point of April 2008 safety review) retrieved 73 cases for analysis.

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

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

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

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

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

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**PSUR (periodic safety update report) update:**

**Gedeon Richter:**

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

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

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

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

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

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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. The Applicant has proposed adding dysmenorrhea and pelvic pain to the Adverse Reaction section of the Plan B label, and the Division has requested that similar information be added to the postmarketing section in the Plan B One-Step label as well. Although I disagree that women under 16 years of age should not take levonorgestrel without medical supervision, this point is moot at this time as the Applicant (Duramed) is seeking prescription approval for women under age 17, so medical supervision would be *de facto* provided to women under age 17.

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Duramed (Plan B):

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

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

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

<b>Table 3.1.A. Distribution of Plan B® Postmarketing Adverse Events by Source, Seriousness and Expectedness during the period July 1, 2007 to June 30, 2008</b>					
	<b>Total AEs</b>	<b>Serious</b>		<b>Non-Serious</b>	
		<b>Expected</b>	<b>Unexpected</b>	<b>Expected</b>	<b>Unexpected</b>
<b>Healthcare Professionals</b>	47	2	5	28	12
<b>Non-Healthcare Professionals</b>	15,385	16	46	11,735	3,588
<b>Total</b>	15,432	18	51	11,763	3,600

<b>Table 3.1.B. Most Frequently Reported Adverse Events by Preferred Term during the Period from July 1, 2007, to June 30, 2008</b>	
<b>Adverse Event Preferred Term</b>	<b>Number of Reports</b>
<b>Gastrointestinal disorders</b>	
Abdominal pain	632
Nausea	1275
Vomiting	603
<b>General disorders and administration site conditions</b>	
Fatigue	486
<b>Nervous system disorders</b>	
Dizziness	515
Headache	562
<b>Reproductive system and breast disorders</b>	
Dysmenorrhoea	653
Menstruation irregular	5505
Oligomenorrhoea	533
Pelvic pain	733
<b>Total</b>	<b>11,497</b>

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

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

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

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

Based on available safety information from this reporting period, the current US prescribing information adequately describes the benefit-risk profile for Plan B."

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

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

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

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

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

**Global Pharmacy and OTC availability:**

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

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

**Scientific Literature since November 2006:**

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

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

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

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

**Overall Safety Conclusion:**

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

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

Furthermore, it is important to note that the original recommendation from DRUP and the Office of Drug Evaluation III for the OTC availability of Plan B was that there did not need to be any age restriction. The joint Advisory Committee that met on December 16, 2003 recommended by a vote of 23 to 4 that Plan B was sufficiently safe to be distributed over-the-counter without any age or distribution restrictions and without any further studies before approval. I continue to believe, based on all the clinical trial results, available medical literature, and postmarketing data, that both Plan B and Plan B One-Step could be safely used by women of all ages in the absence of a "learned intermediary;" i.e., the levonorgestrel emergency contraception is appropriate for OTC marketing to all women of childbearing age regardless of their age.

**7.2 Adequacy of Safety Assessments**

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

**7.4 Supportive Safety Results**

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

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

### **7.6 Additional Safety Evaluations**

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

### **7.7 Additional Submissions / Safety Issues**

There are none.

## **8 Postmarket Experience**

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

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## **9 Appendices**

### **9.1 Literature Review/References**

See discussion under Review of Safety, Section 7.1.

### **9.2 Labeling Recommendations**

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

**Labeling Consultations within the Agency included the following:**

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

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

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

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

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

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

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

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

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

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

3. The Applicant wanted to \_\_\_\_\_

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\_\_\_\_\_ The Applicant acknowledges that levonorgestrel 1.5 mg is marketed worldwide by Gedeon Richter, Schering, and several other companies, but proposed that \_\_\_\_\_

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\_\_\_\_\_ DRUP believes that some postmarketing data for levonorgestrel emergency contraception should be included in the postmarketing section of the prescription label rather than \_\_\_\_\_

\_\_\_\_\_ Final agreement was reached with the Applicant and section **6.2 Postmarketing Experience** reads as follows:

The following adverse reactions have been identified during post-approval use of Plan B (2 doses of 0.75 mg levonorgestrel taken 12 hours apart). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Gastrointestinal Disorders*

Abdominal Pain, Nausea, Vomiting

*General Disorders and Administration Site Conditions*

Fatigue

*Nervous System Disorders*

Dizziness, Headache

*Reproductive System and Breast Disorders*

Dysmenorrhea, Irregular Menstruation, Oligomenorrhea, Pelvic Pain

4. In section **8 Use in Specific Populations**, the Applicant wanted \_\_\_\_\_

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\_\_\_\_\_ In the NDA trial a slightly higher pregnancy rate was seen in Chinese women (1.50%) versus non-Chinese women (1.44%), but it was not statistically significant. The same finding was found in the original Plan B NDA data and it is so labeled. \_\_\_\_\_

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\_\_\_\_\_ Although the reason for the finding is unknown, DRUP and this reviewer believe that such information is helpful to both the prescriber and the consumer and should be included in the

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

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

### **9.3 Advisory Committee Meeting**

In December 2003, an Advisory Committee was held to discuss the switch from prescription status to OTC status for two-dose Plan B (NDA 21-045). As noted earlier in this review, the Committee recommended by a vote of 23 to 4 that Plan B was sufficiently safe to be distributed over-the-counter without any age or distribution restrictions and without any further studies before approval. At this time there is no indication for a second Advisory Committee meeting for the same issue since the two products are practically the same. Plan B has been marketed as an OTC product for women age 18 and older in the United States since the approval in August 2006.

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/s/

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

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

## **Memorandum**

**Date:** July 8, 2009

**From:** Christina Chang, M.D., M.P.H.  
Medical Officer  
Division of Nonprescription Clinical Evaluation (DNCE)

**Through:** Lesley-Anne Furlong, M.D.  
Clinical Team Leader  
Division of Nonprescription Clinical Evaluation (DNCE)

**Subjects:** CARE program submissions for:  
NDA 21-045 Plan B, SE5/015 (Efficacy Supplement)  
NDA 21-998 Plan B One-Step, Complete Response

This is a DNCE medical officer's memorandum to address Duramed's submissions pertaining to the CARE program for marketing of both Plan B and Plan B One-Step. After reviewing both documents (both dated July 7, 2009), I have identified no objectionable components in either submission. As stated in my reviews for these two applications, I do not think the program is necessary to ensure safe use of either product. However, since the program is voluntarily put in place, I have no additional comments.

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/s/

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Christina YC Chang  
7/8/2009 01:19:20 PM  
MEDICAL OFFICER

Lesley-Anne Furlong  
7/8/2009 01:31:28 PM  
MEDICAL OFFICER

I concur with Dr. Chang.



## MEDICAL OFFICER'S REVIEW

Department of Health and Human Services  
Food and Drugs Administration  
Center for Drug Evaluation and Research  
Division of Nonprescription Clinical Evaluation (HFD-560)

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<b>NDA#:</b>	<b>21-998</b>
<b>Drug:</b>	<b>Single tablet levonorgestrel 1.5 mg (Plan B One-Step)</b>
<b>Dosage Form:</b>	<b>Tablet</b>
<b>Pharmacologic Category:</b>	<b>Progestogen</b>
<b>Sponsor:</b>	<b>Duramed</b>
<b>Indications:</b>	<b>Emergency contraception</b>
<b>Document:</b>	<b>Complete Response</b>
<b>Submission Date:</b>	<b>January 9, 2009</b>
<b>PDUFA Goal date:</b>	<b>July 12, 2009</b>
<b>Review Date:</b>	<b>July 6, 2009</b>
<b>Reviewer:</b>	<b>Christina Chang, M.D., M.P.H.</b>
<b>Team Leader:</b>	<b>Lesley Furlong, M.D.</b>

### 1. Introduction

This is a DNCE medical officer's review of the proposed over-the-counter labeling submitted as part of the Complete Response (CR) to address a deficiency identified in FDA's Approvable Letter issued November 22, 2006. The Division of Reproductive and Urologic Products (DRUP) is the lead review division for the submission. The present review is confined to the OTC labeling.

Proposed labeling consists of Rx and OTC dual labeling similar to the two-dose levonorgestrel product (Plan B) except for dosing instructions. The application was amended on June 9, 2009, to propose inclusion of women 17 years of age for OTC marketing. The amendment also included a safety update for levonorgestrel.

The Division of Nonprescription Regulation Development (DNRD) and the Division of Drug Marketing, Advertising, and Communications (DDMAC) have also reviewed the proposed OTC labeling. The Division of Medication Errors Prevention and Analysis (DMEPA) reviewed the trade name.

### 2. Background

Plan B One-Step is similar to Plan B, the only OTC product currently marketed for emergency contraception. The dosing regimen for Plan B consists of two doses of 0.75 mg tablets taken 12 hours apart, with the first dose taken as soon as possible within 72 hours of intercourse. Plan B obtained prescription-only (Rx) status on July 28, 1999. During the review for the OTC switch of Plan B, then CDER Director, Dr. Steven Galson, concluded that the data provided would

support approval for OTC use for women 17 and older, but not for adolescents 16 and younger.<sup>1</sup> Dr. Andrew von Eschenbach, then Acting FDA Commissioner, concurred that the data supported approval for OTC use for women 17 and older, but concluded that, due to enforcement issues, the appropriate age for OTC access should be 18.<sup>2</sup> On August 24, 2006, FDA approved over-the-counter (OTC) marketing for women 18 and older, thus creating a unique dual-marketing distribution status.

Plan B One-Step is a single dose version of Plan B. On January 24, 2006, Duramed submitted NDA 21-998 to DRUP, proposing to market the single-dose regimen of 1.5 mg levonorgestrel as a prescription-only product. The 2006 application supported the safety of the single dose regimen with the results of two large clinical trials (N= 1,906 women in single dose treatment arms), and postmarketing data from an estimate<sup>7</sup> ——— sales of the single dose product in 27 countries. Following publication of the results of the two large clinical trials in 2002, experts in contraceptive technology began to recommend the off-label use of Plan B as a two-tablet, single dose regimen. FDA has monitored the postmarketing safety of Plan B since its approval in 1999, and Plan B continues to demonstrate satisfactory postmarketing safety.

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In November 2006, the Agency determined that Plan B One-Step was safe and effective. However, because the related product, Plan B, was OTC for women aged 18 and older, the Agency also determined that Plan B One-Step, a simpler regimen, could be used safely and effectively as an OTC product by women aged 18 and older. Therefore, FDA took an Approvable Action on November 22, 2006. The deficiencies cited in the Action Letter were the 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”
- “your plan regarding distribution of both the Rx and OTC versions of your product”

Duramed submitted a Complete Response to NDA 21-998 on January 9, 2009.

On March 23, 2009, United States District Court Judge Edward Korman issued an order directing the Agency to permit Duramed to make Plan B available to women 17 and older without prescription within 30 days. In addition, Judge Korman also ordered FDA to reconsider whether to approve Plan B for OTC status without age or point-of-sale restriction.

On April 21, 2009, Dr. Andrea Leonard-Segal, Director of FDA’s Division of Nonprescription Clinical Evaluation, sent a letter to Duramed concluding that Plan B may be made available to women 17 years and older without a prescription, and that Duramed could pursue the change in labeling by submitting revised draft labeling for review. In her letter, Dr. Leonard-Segal noted that the Agency had previously determined data supported the safety of Plan B as an OTC product for women 17 years or older. Furthermore, Dr. Leonard-Segal had considered the previous Acting Commissioner’s enforceability concerns and was unaware of data supporting a

<sup>1</sup> Memorandum by Dr. Steven Galson, dated August 26, 2005.

<sup>2</sup> Letter to Duramed from Dr. Andrew von Eschenbach, dated July 31, 2006

distinction between ages 17 and 18 in terms of enforceability of an age restriction. Finally, data submitted by Duramed from the Convenient Access Responsible Education (CARE) program supported the fact that pharmacists were able to check identification for the age restriction. Dr. Leonard-Segal concluded that Plan B may be made available to women 17 years and older without a prescription.

*Medical officer comment:*

*I agree with Dr. Leonard-Segal's conclusion that Plan B may be made available to women 17 and older without a prescription. I also believe that this conclusion can be applied to Plan B One-Step.*

Following Judge Korman's order, Duramed met with the Agency on June 1, 2009, and stated their intention to pursue dual labeling with OTC access for women aged 17 and older by submitting amendments to both Plan B and Plan B One-Step. The revised labeling for Plan B One-Step was submitted on June 9, 2009.

### **3. Review of Submission**

#### Safety Update

Duramed submitted a safety update on levonorgestrel used as an emergency contraception in the June 9, 2009 amendment. The content is currently under review in DRUP. At the time of this review, no new safety concerns had been detected.

#### Trade name

DMEPA objects to the trade name "Plan B" citing concern for increased confusion with Plan B resulting in medication errors. The second trade name proposed by the sponsor, "Plan B One-Step," is acceptable to DMEPA.

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#### Findings relevant from NDA 21-045 (Plan B), supplement-011 for OTC switch

1. All reviewers up to the level of Center Director (Dr. Galson) concluded that data submitted by the sponsor met the statutory standard for approval for women 17 years and older.
2. The joint session of the Nonprescription Drug Advisory Committee and Advisory Committee of the Reproductive and Urologic Drugs voted overwhelmingly in favor of the Rx-to-OTC switch without age restriction:

Question: Are the Actual Use Study data generalizable to the overall population of potential non-Rx users of Plan B?

Yes = 27                      No = 1

Question: Do you recommend Plan B be switched from prescription to non-prescription status?

Yes = 23                      No = 4 (one member left before voting)

3. The Label Comprehension Study conducted in support of Plan B OTC switch enrolled 656 subjects.<sup>3</sup> Of these, 355 women (54.1%, 355/656) were ages 17 to 25 years. This group met all communication objectives (90% to 96% correct or acceptable).
4. The Actual Use (AU) Study conducted in support of Plan B OTC switch enrolled 585 women aged 14 to 44 years.<sup>4</sup> These women received one pack of Plan B at enrollment, and 540 (92%) used Plan B during the study. Of the 585 women enrolled, 556 (95.0%) were ages 17 to 44 years; 518 out of these 556 (93.2%) actually took Plan B. The pertinent results from the AU study for this age group are as follows:

Overall correct use	68.5%
Correct use of the first pill (< 72 hours)	90.5%
Correct use of the second pill (12 hours after the first pill)	73.7%

There were no serious adverse events reported, nor were new safety signals identified in this four-week study.

*Medical officer comment:*

*With Plan B One-Step having a simpler dosing regimen than Plan B (one dose rather than two), it would appear reasonable to expect women 17 years and older to have a high percentage (at least 90%) of correct use of Plan B One-Step.*

Consumer studies conducted in support of Plan B One-Step OTC status

1. A Label Comprehension Study was conducted by independent investigators whose findings were published in 2009.<sup>5</sup> Since Duramed supplied only the prototype labeling without sponsoring the study, Duramed does not have access to raw data from the study. According to the publication, 171 adolescents aged 15 to 17 years participated in the study. A high proportion of this group understood five of the six key concepts tested (94% to 98%). Although the proportion of these adolescents scored lower on one 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, 86% correctly understood), a high proportion correctly understood the 72-hour time frame (Levonorgestrel 1.5 should be taken within 72 hours after sex, 98%). The authors interpreted this discrepancy to possibly the adolescents' tendency for 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.

<sup>3</sup> Label Comprehension Study review, Dr. Karen Lechter & Dr. Toni Piazza Hepp, dated November 5, 2003.

<sup>4</sup> DNCE Medical Officer NDA review, Dr. Jin Chen, dated January 12, 2004.

<sup>5</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.

*Medical officer comment:*

*The proposed OTC label for women 17 years of age and older appears to have incorporated this recommendation by stating under **Directions**:*

*"Take Plan B One-Step as soon as possible within 72 hours (3 days) after unprotected sex."*

2. Duramed has also initiated an Actual Use Study in adolescents 11 to 17 years of age. However, since Plan B One-Step remains an investigational product, enrollment into the AU study has been slower than anticipated.

CARE Program

When Plan B was approved approximately three years ago, the CARE program was put in place to check if pharmacists were able to follow the prescription age requirements of Plan B. The CARE program also had marketing components to increase knowledge about Plan B. Annual reports of the CARE program have been reviewed by DRUP, most recently for the year 2008. Compliance with the age restriction remains excellent (94%) at over 400 monitored pharmacies in 10 states, and the DRUP reviewer has recommended that the program is no longer necessary.

*Medical officer comment: The CARE program has shown that pharmacists have adhered to the dual Rx-OTC labeling of the related product, Plan B. I concur with the DRUP reviewer who has stated that the CARE program is not necessary for the safe use of Plan B. As labeling and packaging of Plan B One-Step will be almost identical except for simpler dosing instructions, a CARE program is unnecessary for Plan B One-Step as well.*

Labeling

1. The sponsor proposed under **Directions**: \_\_\_\_\_ b(4)

*Medical officer comment:*

*Following discussion within DNCE as well as with DRUP, we are recommending the following:*

*"Prescription only for women younger than 17 years of age. If you are younger than 17 years of age, see a healthcare professional."*

2. Duramed proposed the following instruction under **Directions** (in the Consumer Information Leaflet) to women should vomiting occur after taking Plan B One-Step: b(4)

*Medical officer comment:*

*The proposed two-hour time frame is based on the Tmax of Plan B (1.67 hours). This pharmacokinetic information led the World Health Organization expert Working Group to consider two hours sufficient for hormone absorption with no further action necessary if a woman vomits after this time.<sup>6</sup> However, Duramed acknowledged in the submission that the company has not conducted any studies to determine the appropriate management should*

<sup>6</sup> Selected Practice Recommendations for Contraceptive Use, Second Edition: World Health Organization, 2004.

*vomiting occur after taking Plan B or Plan B One-Step. Neither development plan collected efficacy or safety data at 2 hours.*

*Some providers may recommend repeating the dose (with or without an antiemetic), while others may not. Other management options may include another post-coital contraceptive (such as an intrauterine device). Thus, it is unclear what the optimal management option may be.*

*Furthermore, currently approved Plan B label directs the consumers to call a healthcare professional if vomiting occurs within 1 hour of taking either dose of the medication. The sponsor now proposes the 2 hour limit for Plan B as well as for Plan B consumers to repeat the dose after vomiting. There is concern that women may not understand when the second dose should be taken if the first dose is repeated due to vomiting. This newly proposed direction was not assessed in the Label Comprehension Study conducted to support the Plan B application. Given that both Plan B and Plan B One-Step will be marketed simultaneously, it would be prudent to have consistent language for both regimens to minimize confusion.*

*Again, following internal discussion, we recommend the following for Plan B One-Step Consumer Information Leaflet:*

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

3. The DDMAC reviewer noted a number of promotional statements in the consumer leaflet and recommended removal of the statements. The DNRD and DNCE labeling team concurred with removing promotional statements from the consumer leaflet.
4. The package insert for the prescription version Plan B One-Step notes that there was an increased rate of pregnancy among Chinese women in the Plan B One-Step trial. However, the prescription package insert does not limit Plan B to certain racial groups. The DRUP review of the data stated that the pregnancy rate among Chinese women in the Plan B One-Step trial was 1.50%, whereas the pregnancy rate among non-Chinese women was 1.44%. The difference was not statistically significant. The clinical significance, if any, of the difference in point estimates of the pregnancy rates for Chinese and non-Chinese women is unknown.

*Medical officer comment:*

*Because it is unlikely that the information about possible racial differences in efficacy would have any utility to the consumer, the information is unnecessary on the OTC label.*

5. Based on postmarketing information from Plan B, the sponsor has proposed adding two new adverse events – dysmenorrhea and pelvic pain – to the Adverse Reaction section of Plan B prescription label. DRUP has requested that similar information be added to the Postmarketing Experience section of the Plan B One-Step label as well.

*Medical officer comment:*

*According to Dr. Daniel Davis' review<sup>7</sup>, dysmenorrhea and pelvic pain occurred with very rare frequencies (< 1/10,000) in the postmarketing experience of Plan B. These two events are covered by the broader term "lower abdominal pain" already in the OTC label. Therefore, I do not recommend the inclusion of either "dysmenorrhea" or "pelvic pain" in the OTC list of side effects.*

6. There are minor differences between the most common adverse events listed for Plan B and those listed for Plan B One-Step. For example, the list of side effects for Plan B includes vomiting and diarrhea, whereas the list for Plan B One-Step does not. This reflects the types and frequencies of adverse events from different clinical trials.

*Medical officer comment:*

*The two products are sufficiently similar that it would be ideal for the OTC labels to present identical side effect profiles so as to avoid confusion for the OTC consumers.*

*Since nausea is the second most common side effect reported for both products, it would be reasonable to include vomiting in the list of common side effects for both products, despite the relatively low reporting frequency in the development of Plan B One-Step. Including "vomiting" as a side effect is also desirable because the label for Plan B One-Step includes instructions to the consumers (under **Directions**) should vomiting occur.*

*On the other hand,  may be deleted from the list of side effects from both products. The use of progestins is usually associated with decreased gastrointestinal motility, rather than the opposite. Furthermore, the reported frequencies of "diarrhea" were lower (5% in the original Plan B trial<sup>8</sup>, 4% in the Plan B One-Step trial<sup>9</sup>) than the other side effects in the OTC list.*

b(4)

#### **4. Conclusions**

1. Duramed has satisfactorily resolved the labeling deficiency specified in the Approvable Action Letter dated November 22, 2009.
2. Data required to expand the OTC population to include women 17 years of age were already included in the original application of NDA 21-998 as well as in NDA 21-045.
3. The CARE program is not necessary for the safe use of either Plan B or Plan B One-Step.

#### **5. Recommendations**

Pending successful labeling discussion with the sponsor, this reviewer recommends approval of Plan B One-Step with an OTC label for women who are 17 years of age and older.

<sup>7</sup> Clinical Review, Complete Response to November 22, 2006 Action Letter, Dr. Daniel Davis.

<sup>8</sup> Current Plan B label.

<sup>9</sup> Clinical Review NDA 21-998, Dr. Daniel Davis, dated November 22, 2006.

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

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/s/

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Christina YC Chang  
7/6/2009 11:05:53 PM  
MEDICAL OFFICER

Lesley-Anne Furlong  
7/7/2009 07:30:48 AM  
MEDICAL OFFICER

I concur with Dr. Chang's conclusions and recommendations.

**DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)**

**DIVISION DIRECTOR MEMORANDUM**

**NDA** NDA 21-998  
**Type of Application** Original  
**Applicant** Gedeon Richter, LTD  
Budapest, Hungary  
**U.S. Agent** Duramed Research Inc.  
Bala Cynwyd, PA  
**Proprietary Drug Name** Plan B  (proposed) *b(4)*  
**Established Drug Name** Levonorgestrel Tablets (1.5 mg)  
**Drug Class** Progestogen  
**Indication** 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.  
**Route of administration** Oral  
**Dosage Form** Tablet  
**Dosage Strength** Tablet containing 1.5 mg levonorgestrel  
**Dosing Regimen** One tablet as soon as possible within 72 hours after unprotected intercourse or a known or suspected contraceptive failure.  
**CDER Receipt Date** January 24, 2006  
**PDUFA Goal Date** November 24, 2006  
**Date of Memorandum** November 22, 2006  
**Division Director** Scott E. Monroe, MD  
Acting Division Director, DRUP

**1. RECOMMENDATIONS**

**1.1 Recommendation regarding Approvability**

I believe that levonorgestrel tablets, 1.5 mg (NDA 21-998), from the perspective of both safety and efficacy, could be approved for the Applicant's requested indication of "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." From a regulatory perspective, however, I do not believe that NDA 21-998 can be approved as a prescription-only product as requested by the Applicant. Rather, I believe that NDA 21-998, from a regulatory perspective *and* medical perspective, is Approvable.

November 22, 2006

Approval would be contingent upon the Applicant submitting:

- Revised labeling that meets the requirements of marketing of levonorgestrel tablets, 1.5 mg, as a prescription-only product for women aged 17 years and younger and as a nonprescription (OTC) product for women aged 18 years and older
- A plan that addresses how the Applicant proposes to distribute both the prescription and nonprescription versions of the product

## **1.2 Basis for Recommendation regarding Approvability**

Data contained in NDA 21-998 support a determination that a single 1.5 mg levonorgestrel tablet, 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. The Applicant (Gedeon Richter) also has incorporated by reference to NDA 21-045 data concerning actual use and labeling comprehension for levonorgestrel for emergency contraception (Plan B) into the current NDA. Plan B contains the identical drug substance and provides the same total dose, albeit using a regimen of two doses of levonorgestrel (0.75 mg taken 12 hours apart). Plan B is currently approved for marketing as a nonprescription product for women aged 18 years and older and as a prescription-only product for women aged 17 years and younger.

It is my opinion that the data concerning actual use and labeling comprehension for Plan B can be extrapolated to the safe use of the levonorgestrel 1.5 mg tablet as a non-prescription product. Taking a single tablet once (the dosing regimen for the levonorgestrel 1.5 mg tablet) is less complicated than taking two tablets of 0.75 mg levonorgestrel 12 hours apart. Clearly, if women can understand the more complicated dosing regimen for Plan B and can use Plan B in accordance with its nonprescription labeling without the intervention of a physician, they can understand the less complicated dosing regimen for the single-dose product and can use it appropriately without the intervention of a physician. 21CFR§330.10(a)(4)(vi) states "A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs." The current submission provides no evidence to suggest that the different dosing regimen for levonorgestrel 1.5 mg (a single dose) results in an adversely altered safety profile or reduced efficacy, such that the drug should be available only by prescription. I believe that there are sufficient data supporting the safety and efficacy of levonorgestrel 1.5 mg to approve its use as a nonprescription product.

I also 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. Plan B currently is approved as a prescription-only product for women aged 17 years and younger. Since the Applicant has not provided any additional information in NDA 21-998 to specifically support the safety and appropriate use of levonorgestrel 1.5 mg tablets as a nonprescription product in women aged 17 years and younger, I do not believe that the Applicant could obtain unrestricted approval for nonprescription marketing at the present time. I would therefore support approval of an Application that requested nonprescription product availability for women aged 18 years and older and prescription-only availability for women aged 17 years and younger because I believe that a single-dose regimen (a) offers a significant advantage over a two-dose regimen and (b) should be available as a nonprescription product as soon as possible.

The primary Medical Reviewer (Daniel Davis, MD) makes the following recommendation in his review:

*"I recommend that single dose 1.5 mg levonorgestrel be approved as a prescription 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 of all reproductive ages."*

*"I also have reviewed the results of both the Label Comprehension study and the Actual Use study submitted with the Application for two dose levonorgestrel 0.75 mg (Plan B) to switch from prescription status to over-the-counter (OTC) status. These studies support my opinion that the current single dose product should preferably go directly over-the-counter (OTC) without any age restriction. The product fulfills the general criteria for OTC status and it is important that the medication be taken as soon as possible for reducing the chances of becoming pregnant in women of all reproductive ages. The efficacy and safety for single dose 1.5 mg levonorgestrel appear to be the same as for two dose levonorgestrel 0.75 mg (Plan B). There is no need for a learned intermediary before buying and taking the medication, and compliance for the single dose regimen should be much better than for the two dose regimen for Plan B (12 hour dosing is awkward because of potential night-time dosing)."*

The medical Team Leader (Lisa Soule, MD) includes the following in her recommendation regarding approvability:

*"From the perspective of safety and efficacy, I believe that levonorgestrel 1.5 mg should be approved for marketing. However, from a regulatory perspective, the current application for marketing levonorgestrel 1.5 mg as a prescription-only product is problematic, where there is a very similar product (Plan B) available over-the-counter (OTC) to women aged 18 and up."*

*"Plan B contains the identical drug substance, and provides the same daily dose (albeit using a regimen of two doses taken twelve hours apart). The current submission provides no evidence to suggest that the different dosing regimen for levonorgestrel 1.5 mg (a single dose) results in an adversely altered safety profile, such that the drug should be available only by prescription."*

*"Therefore, I recommend that an approvable action be taken on levonorgestrel 1.5 mg. I recommend that the drug be approved for OTC use by women of reproductive ability without age restriction, subject to submission of revised labeling that meets the requirements of marketing of levonorgestrel 1.5 mg as an OTC product for women of all ages."*

Both the primary Medical Reviewer and the medical Team Leader have concluded that levonorgestrel tablets, 1.5 mg, are safe and effective for emergency contraception to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Both also believe that to obtain optimal efficacy, the tablet should be taken as soon as possible within 72 hours of intercourse. I concur with these conclusions.

Dr. Davis believes that the current Application for prescription-only marketing can be approved. I do not concur with his recommendation for the reasons previously provided. Dr. Davis also recommends that the single-dose product should preferably go directly OTC without any age restriction. Dr. Soule recommends that the Applicant submit revised labeling that meets the

requirements for marketing of levonorgestrel 1.5 mg as an OTC product for women of all ages. I do not disagree with their similar positions from a pure safety and efficacy perspective. However, I do not believe that an amended Application for OTC use without any age restriction, in the absence of additional data specifically to support the safety and appropriate use of levonorgestrel 1.5 mg tablets as a nonprescription product in women aged 17 years and younger, would receive Agency approval at the present time. Consequently, I do not support their recommendation at this time because, as stated earlier, I believe that a single-dose regimen (a) offers a significant advantage over a two-dose regimen and (b) should be available as a nonprescription product as soon as possible.

### **1.3 Recommendation on Risk Management Steps and/or Phase 4 Studies**

#### **1.3.1 Recommendation on Risk Management Steps**

No clinically significant safety signals have been identified with the use of the currently marketed prescription/OTC product (Plan B), in the foreign postmarketing safety data pertaining to the single-dose product provided by the Applicant, or in the primary clinical trial WHO 97902 and the single supportive clinical trial conducted in Nigeria<sup>1</sup> for the proposed single-dose regimen. I believe levonorgestrel 1.5 mg tablet, from a pure safety and efficacy perspective, is sufficiently safe to be available as a non-prescription product to postmenarcheal women of all ages. However, because I do not believe that the Applicant can obtain regulatory approval at the present time for non-prescription marketing of levonorgestrel 1.5 mg tablets for postmenarcheal women age 17 years or less, the Applicant will need to submit a plan that addresses how both the prescription and nonprescription versions of the product will be distributed.

#### **1.3.2 Phase 4 Studies**

No Phase 4 studies are recommended at this time.

## **2. BACKGROUND**

### **2.1 Available Therapies for Emergency Contraception**

Preven, an emergency contraceptive prescription product containing levonorgestrel (hereafter referred to as LNG) and ethinyl estradiol, was approved in 1998, but subsequently taken off the market in 2005 for business considerations. Currently, the only available product specifically approved for emergency contraception is Plan B, a product that consists of two 0.75 mg tablets of LNG that are taken 12 hours apart starting within 72 hours of intercourse. In August 2006, Plan B was approved in the US as a non-prescription product for women aged 18 years and older and a prescription-only product for women aged 17 years and younger.

### **2.2 Description of Drug Product**

The proposed drug product consists of a single 1.5 mg oral tablet of LNG 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. Levonorgestrel 1.5 mg tablets are approved for emergency

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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.

contraception in over 20 countries (including Brazil, Bulgaria, Denmark, Dominica, Estonia, the European Union, France, Netherland-Antilles, Hungary, Ireland, Jamaica, Latvia, Luxemburg, Peru, Poland, Portugal, Russia, Slovakia, Spain, the United Kingdom and Venezuela) according to the Applicant.

### 2.3 Regulatory History

Plan B (consisting of a total of two 0.75 mg LNG tablets that are to be taken 12 hours apart) was approved for marketing in the U.S. in July 1999 as a prescription-only product. A supplement to switch the product from prescription to non-prescription status for postmenarcheal women of all ages was submitted to the Agency in April 2003. This supplement was not approved by the Director of the Center for Drug Evaluation and Research (CDER) in May 2004, who stated that the supplement did not provide sufficient data demonstrating the safety and efficacy of the product for non-prescription use by women under the age of 16 years. The Applicant submitted a Complete Response in July 2004, proposing a change in product marketing to non-prescription status for women aged 16 years and older, while maintaining prescription-only status for women less than 16 years of age. On August 24, 2006, the Applicant was issued an Approval Letter to market Plan B as a non-prescription product for women aged 18 years and older and as a prescription-only product for women aged 17 years and younger.

During the period in which the Plan B Application (i.e., the Complete Response) for non-prescription marketing was under review, a preNDA meeting between the Division of Reproductive and Urologic Products (DRUP) and the Applicant was held in January 2006 to discuss the Applicant's plan to submit an NDA for a single-dose version of Plan B. On January 24, 2006, the Applicant submitted NDA 21-998, proposing a single-dose regimen of 1.5 mg LNG as a prescription-only product for the indication of emergency contraception. This proposal for prescription-only marketing mirrored the availability of Plan B at the time of submission of the NDA.

### 3. OVERVIEW OF CLINICAL PROGRAM

The Applicant has submitted data from a large randomized, double-blind, multicenter World Health Organization (WHO) trial (Study 97902). This trial randomized 4,136 women who presented within 120 hours after unprotected intercourse to one of three arms – LNG 0.75 mg, administered in two 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) two dosing regimens for LNG when administered either as two doses of 0.75 mg 12 hours apart (i.e., the regimen of Plan B) or as one dose of 1.5 mg 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 three emergency contraceptive regimens, the clinical reviews focus on the effectiveness of the two different dosing regimens for LNG because the Applicant is not seeking approval for mifepristone.*
- *Additionally, although women were randomized if they presented within 120 hours of unprotected intercourse, the Applicant is requesting an indication for use only within*

*72 hours after unprotected intercourse; therefore, the clinical review of the medical Team Leader and this Memorandum focus primarily on efficacy when the two LNG dosing regimens are initiated within 72 hours after intercourse.*

- *DRUP agreed to accept one adequate and well-controlled study as adequate proof of safety and effectiveness because one LNG 1.5 mg tablet is the same total dose as two LNG 0.75 mg tablets taken 12 hours apart (the presently approved Plan B product).*

Supportive efficacy and safety information was provided based upon the publication of Arowajolu AO et al., a study conducted in Nigeria comparing the safety and efficacy of the two-dose regimen of LNG 0.75 mg with a single-dose of 1.5 mg LNG. In this study, 1,160 women presenting within 72 hours of unprotected intercourse were randomized into one of the two treatment regimens.

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.

In addition, two clinical pharmacology studies were submitted, a cross-over bioavailability study comparing the pharmacokinetic (PK) parameters of levonorgestrel 1.5 mg administered once as compared to levonorgestrel 0.75 mg administered as two tablets 12 hours apart (Study 2162) and a cross-over bioequivalence study (Study 2990) comparing the C<sub>max</sub> and AUC values for LNG 1.5 mg administered in a single tablet (the to-be-marketed product) compared to LNG 1.5 mg administered as two 75 mg tablets at the same time (the product used in the primary Phase 3 clinical trial).

#### **4. EFFICACY**

##### **4.1 Primary Clinical Study – WHO Study 97902**

##### **4.1.1 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 day of their 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 chance of conception on different days of the cycle was based on probabilities obtained by two methods: the one of Dixon et al (1980)<sup>2</sup> and the one attributable to Wilcox et al (1995)<sup>3</sup>. The pregnancy rate (PR), or percentage of women who became pregnant,

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2 Dixon GW et al. Ethinyl estradiol and conjugated estrogens as postcoital contraceptives. JAMA 244:1336-9, 1980.

3 Wilcox AJ et al. Timing of intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. N Engl J Med 333:1517-21, 1995.

and its 95% confidence interval, also was calculated. No formal statistical comparisons or threshold to meet were planned for the study.

#### 4.1.2 Study Population and Subject Disposition

This trial was conducted in a total of 15 family-planning clinics in China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland, and the UK. Counting only the women who enrolled within 72 hours of unprotected intercourse, the WHO study enrolled 1,218 women into the single-dose regimen of LNG, and 1,203 women into the two-dose regimen. Excluding 40 women who were lost to follow-up or considered nonevaluable, (20 or 1.6% of the subjects in the single-dose arm and 20 or 1.7% of the subjects in the two-dose arm), the efficacy populations consisted of 1,198 women in the single-dose regimen and 1,183 women in the two-dose regimen. The ethnic status of the subjects in the two LNG treatment groups is summarized in Table 1.

**Table 1 Ethnic Status of Subjects enrolled into WHO Trial 79702\***

Ethnic Group	Single-Dose Group N=1198		Two-Dose Group N=1183	
	n	%	n	%
Chinese	667	55.7	648	54.8
Asian/Black	130	10.9	137	11.6
Caucasian	401	33.5	398	33.6

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

Source: Modified from Table 1 of medical Team Leader review.

#### 4.1.3 Principal Efficacy Findings

The efficacy findings, including analyses of subsets, are presented in detail in the reviews of the primary Medical Reviewer, medical Team Leader, and FDA biostatistician. The following is a brief overview of the primary efficacy findings.

##### Primary Efficacy Analysis

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 2). The overlapping confidence intervals for the two dosing regimens indicate that the difference in prevented fraction of expected pregnancies was not statistically significant.

**Table 2 Efficacy Results (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
Single-Dose	1198	16	1.34	0.77	2.16	99.7	83.95	73.94	90.83
Two-Dose	1183	20	1.69	1.04	2.60	94.9	78.92	67.44	87.12

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

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

Source: Modified from Table 4, medical Team Leader Review.

**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 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 two dosing regimens. The adjusted RR, which controlled for the number of expected pregnancies in each group, was similar (see Table 3).

**Table 3 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
Single-Dose vs. Two-Dose	0.7900	0.4114	1.5170	0.7612	0.3690	1.5438

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

Source: Modified from Table 5, medical Team Leader Review.

**Effect of Time of Treatment Onset.** Efficacy stratified by the time of presentation for emergency contraception was evaluated (see Table 4). The prevented fraction of expected pregnancies with each regimen was lower among the combined women treated four or five days following unprotected intercourse as compared to those treated within the first three days after the encounter. There was a statistically significant decrease in efficacy, as assessed by the pregnancy rate, seen only when comparing women who were treated more than 96 hours after intercourse to those treated within 0-96 hours of unprotected coitus.

**Table 4 Efficacy Analysis by Time of Treatment in WHO Study 97902 (ITT Population)**

LNG Group	N	Observed Pregnancies				Prevented Fraction (%) of Expected Pregnancies			
		#	Rate	95% LL	95% UL	# Preg. Expected	PF*	95% LL	95% UL
<b>Treatment within 1-3 days of unprotected intercourse</b>									
Single-Dose	1198	16	1.34	0.77	2.16	99.7	83.95	73.94	90.83
Two-Dose	1183	20	1.69	1.04	2.60	94.9	78.92	67.44	87.12
<b>Treatment within 4-5 days of unprotected intercourse</b>									
Single-Dose	150	4	2.67	0.73	6.69	10.7	62.51	4.01	89.79
Two-Dose	164	4	2.44	0.67	6.13	9.9	59.62	0	89.0

\* PF: prevented fraction of expected pregnancies.

Source: Modified from Table 6, medical Team Leader Review.

#### 4.1.4 Statistical Reviewer's Assessment

Sonia Castillo, PhD., FDA biostatistician, stated the following in the Conclusion of her review (signed on September 26, 2006):

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

#### Division Director's Comment

- *The values cited by Dr. Castillo are based on the ITT population for women who took a single-dose of levonorgestrel 1.5 mg from 0 to 120 hours after unprotected intercourse.*

#### 4.2 Supportive Efficacy Data

In the study conducted in Nigeria (Arowojolu AO et al.), 1160 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 pregnancies (0.98% overall rate) were reported (4 in the single-dose group; 7 in the two-dose group (see Table 5). 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 5 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	95% UL
Single-dose	573	4	0.69	0.02	1.38	57.1	92.99	81.25	97.38
Two-dose	545	7	1.28	0.34	2.20	53.1	86.80	72.07	93.77

\* PF: Prevented fraction of expected pregnancies.  
Modified from Table 12 of Primary Medical Review.

**Division Director's Comments**

- *The findings here are based entirely on the publication of the results from the large, blinded, comparative Nigerian study. The original datasets and CRFs were not submitted as part of the NDA.*
- *The findings are similar to those of WHO Study 97902 in that the value for prevented fraction of expected pregnancies for the single-dose regimen suggests slightly better contraceptive effectiveness than that for the two-dose regimen.*

**4.3 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 had a slightly better, but not statistically significant, effectiveness (83.95% of expected pregnancies prevented) than the two-dose 0.75 mg LNG regimen (78.92% of expected pregnancies prevented) when taken within 72 hours of unprotected intercourse. A trend towards a lower efficacy with a longer delay in taking LNG after unprotected intercourse was evident when considering the pregnancy rates for the two 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.

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.
- 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 LNG 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.

**5. SAFETY FINDINGS**

**5.1 Primary Clinical Study – WHO Study 97902**

In WHO Study 97902, all women who had received at least one dose of study medication were included in the safety analysis. All women took the first dose of study medication under direct

observation; thus, 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.

Subjects were asked to keep a diary of side-effects in the week after treatment and to record spotting or bleeding, acts of intercourse, and whether a condom was used, until their next menses or the follow-up visit, whichever came first. Expected side effects were listed on the diary card to be checked if they occurred; additional comments also were allowed to be written on the diary card.

#### 5.1.1 Deaths and Other Serious Adverse Events

There were no deaths in the clinical trial.

In subjects taking LNG, there were three reports of serious adverse events during the study. In the LNG single-dose group, two serious adverse events were reported:

- Subject 1340/0013-R, age 28, developed a corpus luteum cyst, was hospitalized, and had a laparoscopy for a ruptured cyst eight days after taking LNG.
- Subject 0001/0213-C had an acute appendicitis, was hospitalized, and underwent surgery.

In the LNG two-dose group, Subject 0001/0009-W, age 26, had an ectopic pregnancy diagnosed by the absence of an amniotic sac and an increasing serum hCG level. A complete post-operative recovery was reported.

According to the primary Medical Reviewer, there was one ectopic pregnancy and 44 documented pregnancies in women taking LNG (single- or two-dose regimens) in the primary trial. In his review he makes the following statement:

*"1-2% of all pregnancies are expected to be ectopic. The occurrence rate of one ectopic out of 44 pregnancies is 2.2%, slightly above the expected range. If the findings from the Nigerian trial (11 pregnancies with no ectopic pregnancies) are added to the WHO Study data, the incidence drops to 1.8% (1/55). These findings do not raise a safety issue and there is no signal that women who use levonorgestrel for emergency contraception have an increased absolute rate of ectopic pregnancy."*

#### Division Director's Comments

- *The study investigators and the FDA primary Medical Reviewer assessed that the appendicitis and ruptured corpus luteum cyst were not due to treatment with LNG.*
- *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. He concluded that based on available data there were no concerns about the safety of Plan B.*

There were 41 women who took at least one dose of LNG and were lost to follow-up, but there were no subjects who were documented to have terminated from the trial because of an adverse event. The percentage of subjects who were lost to follow-up was 1.5%.

#### 5.1.2 Common Adverse Events

A total of 695 women who received the single-dose regimen and 693 women receiving the two-dose regimen (50% of each group) 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 6). The incidence of AEs did not differ between the two LNG treatment regimens.

**Table 6 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: Primary Medical Review, dated November 22, 2006, Table 15.

**Division Director's Comment**

- *The incidence of common AEs did not differ between the two LNG treatment regimens.*

**Alteration in Menstrual Bleeding Pattern.** Use of LNG for emergency contraception can result in an alteration in the timing of 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 seven or more days beyond the expected date of menses. Women were asked to characterize their period following treatment as "less, similar, more, or much more" than their normal menses. 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.

**5.2 Supportive Safety Data**

**5.2.1 Nigerian Clinical Trial**

The most frequently reported adverse events in the Nigerian study were nausea, vomiting, dizziness, headache, breast tenderness, lower abdominal pain, and menorrhagia (see Table 7).

**Table 7 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
Vomiting	8.4	7.8
Dizziness	13.9	12.6
Headache	14.5	21.3
Breast tenderness	8.8	12.9
Lower abdominal pain	18.3	15.6
Heavy menses	10.5	15.5

Source: Table 13, medical Team Leader review, dated November 22, 2006.

### 5.2.2 Postmarketing Safety Data

#### Postmarketing Safety Update from the Applicant

A safety update was submitted by the Applicant providing a periodic safety update report 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 medical 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 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."*

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

- I have also reviewed the September 2006 data provided by the 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.*

### **5.2.3 Reference to NDA 21-045 (Actual Use and Label Comprehension Studies)**

The Applicant (Gedeon Richter) has incorporated, by reference to NDA 21-045, data concerning actual use and labeling comprehension for levonorgestrel for emergency contraception (Plan B) into the current NDA. During the Agency's review of NDA 21-045 for marketing approval for Plan B as a nonprescription product for women of all ages, Dr. Davis, reviewers from the Division of Nonprescription Products (DNP) and others (including myself), reviewed an actual use study and a label comprehension study for Plan B. The results of these studies also were presented to an FDA Advisory Committee. Both Dr. Davis and myself, reviewers from the DNP, and the Advisory Committee concluded that Plan B, based on review of these and other studies, was sufficiently safe for marketing as a nonprescription drug product for postmenarcheal women of all ages.

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

- *It is my opinion that the data concerning actual use and labeling comprehension for Plan B can be extrapolated to the safe use of the levonorgestrel 1.5 mg tablet as a non-prescription product. Taking a single tablet once (the dosing regimen for the levonorgestrel 1.5 mg tablet) is less complicated than taking two tablets of 0.75 mg levonorgestrel 12 hours apart. Clearly, if women can understand the more complicated dosing regimen for Plan B and can use Plan B in accordance with its nonprescription labeling without the intervention of a physician, they can understand the less complicated dosing regimen for the single-dose product and can use it appropriately without the intervention of a physician.*
- *Based in part on these data, 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.*

### **5.3 Overall Assessment of Safety Findings**

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 per dose taken 12 hours apart), which has been determined to be sufficiently safe for non-prescription marketing for women aged 18 years and older in the U.S. In the clinical trial safety data for the LNG single-dose regimen, there were no serious adverse events likely to be attributable to the drug. The Gedeon Richter postmarketing safety data (based upon more than \_\_\_\_\_ uses of LNG emergency contraception between January and July 2006) and the FDA's AERS database reports (based upon \_\_\_\_\_ U.S. uses of Plan B since

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**Levonorgestrel Tablets 1.5 mg**

approval for marketing) do not suggest any clinically significant safety concerns for LNG used for emergency contraception.

#### **6. OTHER DISCIPLINES**

There are no unresolved issues other than labeling; labeling will be addressed during the next review cycle.

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.

#### **7. LABELING**

Labeling issues will be addressed during the next review cycle.

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/s/

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Scott Monroe  
11/22/2006 03:35:33 PM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type NDA  
Submission Number 21-998  
Submission Code N-000

Letter Date Jan-24-2006  
Stamp Date Jan-24-2006  
PDUFA Goal Date Nov-24-2006

Reviewer Name Daniel Davis, MD, MPH  
Review Completion Date Nov-22-2006

Established Name Levonorgestrel 1.5 mg tablet  
(Proposed) Trade Name Plan B            b(4)  
Therapeutic Class Emergency Contraception  
Applicant Gedeon Richter, Ltd (Budapest, Hungary)  
U.S. Agent Duramed Pharmaceuticals, Inc.

Priority Designation S

Formulation Oral tablet  
Dosing Regimen One tablet as soon as possible  
Indication Emergency contraception  
Intended Population Women of reproductive age

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

I recommend that single dose 1.5 mg levonorgestrel be approved as a prescription 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 of all reproductive ages.

I also have reviewed the results of both the Label Comprehension study and the Actual Use study submitted with the Application for two dose levonorgestrel 0.75 mg (Plan B) to switch from prescription status to over-the-counter (OTC) status. These studies support my opinion that the current single dose product should preferably go directly over-the-counter (OTC) without any age restriction. The product fulfills the general criteria for OTC status and it is important that the medication be taken as soon as possible for reducing the chances of becoming pregnant in women of all reproductive ages. The efficacy and safety for single dose 1.5 mg levonorgestrel appear to be the same as for two dose levonorgestrel 0.75 mg (Plan B). There is no need for a learned intermediary before buying and taking the medication, and compliance for the single dose regimen should be much better than for the two dose regimen for Plan B (12 hour dosing is awkward because of potential night-time dosing).

### **1.2 Recommendation on Postmarketing Actions**

Levonorgestrel 1.5 mg (divided into two 0.75 mg tablets taken 12 hours apart), marketed as Plan B, was approved in the U.S. in July 1999 and has been used extensively since then. Furthermore, a dose of 1.5 mg levonorgestrel is approved globally in over 100 countries for emergency contraception and has seen widespread use both as a two-dose regimen and in 27 countries as a single dose regimen. The single dose regimen is available directly from a pharmacist without a physician's prescription in eight countries and truly over-the-counter in two countries (Sweden and Netherlands). Because of the extensive worldwide experience with levonorgestrel 1.5 mg for emergency contraception, the well-established safety profile, and minimal adverse event reports made to the FDA and to Gedeon Richter, Ltd, no postmarketing actions are recommended at this time.

#### **1.2.1 Risk Management Activity**

The safety of levonorgestrel in lower doses in oral contraceptive pills taken for routine contraception and in the higher (1.5 mg) dose for emergency contraception has been well established. There are no signals in the current NDA or from worldwide postmarketing reports that suggest the single dose regimen will have a different safety profile from the two dose regimen. For these reasons, no risk management activity is recommended.

#### **1.2.2 Required Phase 4 Commitments**

None are required or recommended.

#### **1.2.3 Other Phase 4 Requests**

Plan B 0.75 mg (two-dose) levonorgestrel was approved in August 2006 for over-the-counter (OTC) distribution specifically in pharmacies and clinics for women age 18 and older. If interested, the Applicant will also need to explore what will be needed to remove any FDA imposed age restriction and distribution restrictions on the OTC availability of Plan B and single dose 1.5 mg levonorgestrel.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

Teleconferences with the Applicant were held in November 2005 and January 2006 to discuss the requirements for this NDA submission. There is one large World Health Organization (WHO) study that was submitted with the NDA. WHO Study 97902 was carried out between 1998-2001 at 15 foreign medical centers, 14 of which have been involved with WHO-sponsored reproductive studies on several occasions. It was felt by the Division that inspections were not indicated because these centers had been routinely monitored throughout this and previous WHO trials, and because the original case report forms (CRFs) were part of the NDA submission. The randomized, double-blind, multinational, parallel group WHO study compared three active treatment regimens for emergency contraception administered as follows:

- (i) two 5 mg tablets (10 mg dose) of mifepristone plus one placebo dose taken 12 hours later;
- (ii) two single doses of 0.75 mg of levonorgestrel taken 12 hours apart (total dose of 1.5 mg); and
- (iii) one dose of 1.5 mg of levonorgestrel taken as two 0.75 mg tablets plus one placebo dose taken 12 hours later.

The treatment regimens were given orally during only one treatment cycle, with the first dose swallowed in the presence of a member of the study team, who recorded the date and time of administration, and the second dose taken off-site 12 hours later. Women requesting emergency contraception within 120 hours of unprotected intercourse who satisfied the standard inclusion criteria, which included a negative pregnancy test and willingness to abstain from further acts of intercourse during that cycle, were randomly assigned to a treatment group. More than 4,100 women participated in the trial; 2,756 women took at least one dose of levonorgestrel for emergency contraception.

A literature publication was submitted from a randomized, double-blind, comparative trial in Nigeria for women requesting emergency contraception within 72 hours after unprotected intercourse. Six hundred women took the single dose 1.5 mg levonorgestrel and 560 women took the two doses of 0.75 mg levonorgestrel taken 12 hours apart. The levonorgestrel tablets for the Nigerian trial were manufactured by Gedeon Richter, the Applicant and manufacturer of the levonorgestrel product for this current NDA.

#### 1.3.2 Efficacy

The two levonorgestrel regimens are highly effective for emergency contraception. The WHO 97902 study showed that in the full ITT population of over 2,700 women the single dose 1.5 mg levonorgestrel regimen had a slightly better, but not statistically significantly different, effectiveness (82% of expected pregnancies prevented) compared to the two dose 0.75 mg levonorgestrel (77% of pregnancies prevented). A trend towards a lower efficacy with a longer delay in taking the levonorgestrel drug after unprotected intercourse was evident when considering the pregnancy rates for two time intervals (initiation of treatment between 0 to 72 hours of unprotected intercourse and from 73 to 120 hours).

The Arowojolu et al. study in Nigeria<sup>1</sup> is supportive of the effectiveness of both levonorgestrel regimens taken within 72 hours of unprotected intercourse. It also supports the first three comments that are listed below. Concerning efficacy it is important to emphasize the following:

1. Taking emergency contraception as soon as possible after unprotected intercourse and within 72 hours of the event will optimize pregnancy prevention.

<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* 2002;66:269-273.

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

### 1.3.3 Safety

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

### 1.3.4 Dosing Regimen and Administration

A single tablet containing 1.5 mg levonorgestrel is taken orally as soon as possible within 72 hours of a known or suspected contraceptive failure (such as a broken condom) or unprotected intercourse (no birth control method used). A repeat dose may be taken within the same menstrual cycle or a future cycle, but emergency contraception is NOT intended for routine use for contraception.

### 1.3.5 Drug-Drug Interactions

No special studies have been performed.

### 1.3.6 Special Populations

No studies have been done in special populations. Use in hepatic and renal impaired women has not been studied; it is unknown if these conditions affect the efficacy and safety of single dose 1.5 mg levonorgestrel.

The product is not indicated in premenarcheal adolescents because they are not at risk for pregnancy. Specific studies in postmenarcheal adolescent studies have not been done, but the WHO study included girls as young as 14. In addition, it has generally been demonstrated that the safety, effectiveness and mechanisms of action of both routine and emergency hormonal contraception are the same for young adolescents as they are for older adolescents. The Applicant has requested a waiver of pediatric studies and the reviewer agrees that this waiver should be granted.

Contraceptive effectiveness appears to be slightly lower in Chinese women. The reasons for this finding are not known, but this finding is included in the proposed product labeling. There are adequate controlled clinical data with African women from the Nigerian trial and Caucasian women from the large WHO Study 97902. Clinical trial data from Hispanic women is very limited, but there is no evidence based on the use of two dose 0.75 mg levonorgestrel that safety and efficacy are different in this population.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

From the time of launch in the United States in August 2000 until August 31, 2006, Plan B (two 0.75 mg levonorgestrel tablets taken 12 hours apart) has sold over \_\_\_\_\_ units. The projected U.S. use for 2006 is over \_\_\_\_\_ units (based on \_\_\_\_\_ units in the first 8 months).

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### 2.2 Currently Available Treatment for Indications

Preven™, an emergency contraceptive prescription product containing levonorgestrel and ethinyl estradiol, was approved in 1998, but taken off the market in 2005 purely for business reasons. There are 22 prescription combination oral contraceptive pills (containing both levonorgestrel and ethinyl estradiol) that may be taken for emergency contraception with a two dose, 12-hour dosing regimen. Currently the only available dedicated product for emergency contraception in the U.S. is Plan B, containing two levonorgestrel 0.75 mg tablets to be taken 12 hours apart. In August 2006, Plan B was approved for OTC use in women age 18 and over; it remains a prescription product for women under age 18. Product launch for OTC availability was initiated in November 2006.

### 2.3 Availability of Proposed Active Ingredient in the United States

Levonorgestrel is readily available in the U.S. in several combination oral contraceptive pills, progestin-only contraceptive pills (so-called "mini-pill"), and Plan B for emergency contraception.

### 2.4 Important Issues with Pharmacologically Related Products

Levonorgestrel is considered to be a progestin hormone. For products containing a progestin only and used as a single use treatment, there are no issues of concern. There is a well-established favorable safety profile for progestin-only drugs, especially when limited to a single dose.

### 2.5 Presubmission Regulatory Activity

Duramed Pharmaceuticals, Inc. (the agent for Gedeon Richter, hereafter, the Applicant) had a teleconference with the Office of Drug Evaluation (ODE) III Director on 11-29-05 to discuss their intention to submit an NDA for the single dose 1.5 mg levonorgestrel product. The Applicant was advised to submit an NDA distinct from the Plan B NDA and to request a pre-NDA meeting with DRUP (the Division of Reproductive and Urologic Products). The pre-NDA meeting with DRUP was held on 1-13-06 and agreements reached on the format of the electronic submission and the potential acceptability of using the datasets from the WHO randomized, blinded Study 97902. It was agreed that the original datasets from a second trial would not be required. The NDA was submitted on 1-24-06. At the time of this NDA submission in January 2006, Plan B was not approved for OTC marketing; a potential OTC submission for the single dose levonorgestrel product was therefore not discussed with the Applicant.

### 2.6 Other Relevant Background Information

The use of levonorgestrel for routine hormonal contraception, emergency contraception, and post coital routine contraception (in couples with 1-4 acts per month) has been studied for the past 35 years. The safety and efficacy of levonorgestrel in women of reproductive age, whether used alone or in combination with ethinyl estradiol (an estrogen), has been well established. As noted in Section 2.2 above,

levonorgestrel 0.75 mg taken 12 hours apart was approved in August 2006 for OTC distribution; this fact also strongly supports the safety of the use of a total dose of levonorgestrel 1.5mg for emergency contraception.

### **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

#### **3.1 CMC (and Product Microbiology, if Applicable)**

The main issue for the chemistry review was the dissolution specifications for the to-be-marketed product. Additional information requested by DRUP (Division of Reproductive and Urologic Products) and by reviewing chemist Monica Cooper, Ph.D. was received on October 19, 2006. The final conclusion was that the specifications were acceptable and that there were no further chemistry issues that would preclude approval for CMC issues.

#### **3.2 Animal Pharmacology/Toxicology**

No new preclinical data were submitted. The pharmacology/toxicology review by Lynnda Reid, Ph.D. does not note any toxicity issues with the use of levonorgestrel, even at fairly high doses (e.g., 50 times the human equivalent dose in rats), when administered over a short period of time. The overall toxicologic profile for levonorgestrel, including general and genetic toxicology, reproductive toxicology, and carcinogenicity were reviewed by Dr. Reid. Her conclusion is that approval of the levonorgestrel 1.5 mg tablet is recommended.

### **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

#### **4.1 Sources of Clinical Data**

The primary source of clinical data is the randomized, double blind WHO Study 97902 with over 2,700 women using levonorgestrel for emergency contraception. Supportive data is from the randomized, double blind Nigerian study with over 1,100 women using levonorgestrel for emergency contraception for which only the publication was submitted. Both of these trials were blinded and directly compared the single dose and two dose regimens using a total dose of 1.5 mg levonorgestrel. See Table 1 below.

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

#### **4.2 Tables of Clinical Studies**

In Table 1 below, the safety population is the "full intent-to-treat (ITT) population," the number of women who took the study drug and were followed up for at least one visit. The efficacy population is also the "full ITT population." In addition, the Applicant analyzed the "restricted" ITT population which excluded all women with major protocol violations.

Table 1 Clinical Studies Populations

Trial	WHO Study 97902		Nigerian Study	
	Single dose	Two dose	Single dose	Two dose
Safety population	1,356	1,356	550	600
Efficacy population	1,356	1,356	545	573
Restricted population	1,293	1,275	NA*	NA

Source: Medical officer tabulations from Applicant's Summary of Clinical Efficacy. \*NA- not available.

### 4.3 Review Strategy

First, the proposed label for the new single dose product was read and compared to the current Plan B (two dose 0.75 mg levonorgestrel) label. No superiority claims for the single dose over the two dose regimen are made in this application. The two labels are very similar, recommending that the drug be taken within 72 hours of unprotected intercourse (even though the primary study included use up to 120 hours after unprotected intercourse). Next, the summaries of clinical efficacy and safety and the listings were reviewed and considered to be generally adequate. In areas where the information was either unclear or inadequate, the final study report was electronically accessed or the Applicant was requested to submit further data. The original case report forms (CRFs) for each of the pregnancies occurring in the two dose levonorgestrel regimen were reviewed to determine if there were any discrepancies between the Applicant's findings and the FDA clinical reviewer's findings. The NDA review was written following the standard FDA Clinical Review template.

Additional studies (found in the NDA application) and subsequent Applicant submissions that were reviewed include the following:

1. Bioequivalence and bioavailability studies
2. The published article reporting the blinded, prospective Nigerian study (N = 1,100) comparing single dose and two dose levonorgestrel for emergency contraception.
3. Tradename correspondence
4. Data and several tables for the subset of women who took their levonorgestrel within 0-72 hours of unprotected intercourse
5. Plan B safety updates, annual reports, and submissions for the switch to OTC status
6. Periodic Safety Update Report (PSUR) from Gedeon Richter for their global marketing of single dose and two dose levonorgestrel

### 4.4 Data Quality and Integrity

The data quality and integrity is acceptable. Original datasets were submitted as requested. The 15 sites in ten different countries are part of the United Nation's WHO/HRP (Human Reproductive Program) network and have been doing contraceptive trials for many years; the sites are monitored by the WHO periodically. No site inspections were requested by the FDA because it was believed to be unnecessary due to the large size of the blinded and randomized trial that essentially was studying a new regimen for a single use of a proven product (Plan B) for emergency contraception.

#### **4.5 Compliance with Good Clinical Practices**

The WHO study conforms to GCP standards. While the trial was in progress, the trial coordinator and other WHO staff visited trial sites. Principal investigators also monitored their staff, and all but one of the centers had previously participated in multicenter trials of emergency contraception. This trial was not monitored by an external independent committee, because the drugs used were already registered and available for widespread use. Data quality monitoring was done in accordance with the standard operating procedures presently used by the WHO in Geneva.

#### **4.6 Financial Disclosures**

The pivotal WHO clinical trial was performed in 10 countries outside the U.S. and not under an IND. According to the Applicant, financial disclosures are not available. However, under 21CFR §312.120 and §314.106 the Applicant is exempt from providing financial disclosures. The Division agreed to this at the January 13, 2006 meeting with the Applicant.

### **5 CLINICAL PHARMACOLOGY**

#### **5.1 Pharmacokinetics**

Following single dose administration of levonorgestrel (LNG) 1.5 mg tablet in 30 healthy women, the maximum LNG plasma concentration of  $19.14 \pm 9.66$  ng/mL was reached at 1.67 hours (range, 1-4 hours). The mean elimination half-life of LNG following single dose administration of LNG 1.5 mg tablet was 27.5 hours (Applicant Study 2990). Study 2990 also evaluated the BA/BE (bioavailability/bioequivalence) under fasting conditions of one 1.5 mg LNG tablet (the to-be-marketed product) to that of two 0.75 mg tablets of LNG with gelatin (the product used in the WHO trial, and marketed as Plan B in the U.S.), administered in a single dose. The geometric mean ratios of  $C_{max}$ ,  $AUC_t$ , and  $AUC_{inf}$  were within acceptable limits of bioequivalence (i.e., 80-125%). Thus, bioequivalence of the to-be-marketed single dose product with the clinical trial single dose product was established.

#### **5.2 Pharmacodynamics**

No special studies were indicated for this NDA submission or requested by the Division.

#### **5.3 Exposure-Response Relationships**

None were studied.

### **6 INTEGRATED REVIEW OF EFFICACY**

#### **6.1 Indication**

Levonorgestrel 1.5 mg tablet is indicated to reduce the chances of pregnancy after a known or suspected contraceptive failure or unprotected intercourse.

##### **6.1.1 Methods**

The primary datasets and requested CRFs from the WHO Study 97902 were submitted with the NDA. In addition, the Applicant's Summary of Clinical Efficacy contained summary findings from the publication of the blinded, randomized Nigerian study comparing single dose and two dose levonorgestrel for emergency contraception with 1,118 evaluable women. The protocol for the study was very similar to the

WHO Study except that the women were treated within 72 hours of unprotected intercourse and there was not a third treatment arm.

The prevention of pregnancy was the primary efficacy outcome measure in this NDA. All suspected pregnancies were evaluated and documented as to the estimated date of conception (EDC). An ultrasound evaluation of the pregnancy was the primary method used to determine the EDC; secondary methods were the use of the last menstrual period and the known times of intercourse. The actual results of these assessments, information about bleeding and drug intake (reconciled with diary data), information about concomitant medications, and final diagnoses were all recorded on the CRFs. Upon confirmation or exclusion of pregnancy, all required follow-up information was documented on the End of Study CRF page that included menstrual data, pregnancy test and ultrasound results, and investigator remarks.

The prevention of pregnancy results were calculated for the three arms of this blinded study, but only the results for the two levonorgestrel arms (single and two-dose) were reviewed in the NDA. The NDA is not seeking approval of mifepristone for emergency contraception and no comparative claims relative to the use of mifepristone for emergency contraception are made in the NDA.

### 6.1.2 General Discussion of Endpoints

The primary efficacy outcome was prevention of pregnancy. The prevented fraction (PF), or the proportion of expected pregnancies prevented by the treatment, is the primary efficacy variable and is 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 cycle day by the estimated probability of conception on that day of the menstrual 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 risk at different days of the cycle was taken as the conception probabilities obtained by two methods: the one of Dixon et al (1980)<sup>2</sup> and the one attributable to Wilcox et al (1995)<sup>3</sup>. The comparison between observed and expected numbers of pregnancies was made by dividing the number of observed pregnancies by the expected number, and calculating its 95% confidence interval (CI) using the Poisson distribution.

**Reviewer's comment:** The prevented fraction is an excellent measure of efficacy as it takes into account the estimated probability of conception on the day of unprotected sex. Therefore, the risk of pregnancy for each individual woman is weighted accordingly. The method used to calculate the expected number of pregnancies and the 95% confidence interval for the PF is described in detail in Appendix 1 of the Statistical Review by Sonia Castillo, Ph.D. The pregnancy rate (PR), or percentage of women who became pregnant, and its 95% confidence interval were also calculated, but, in this reviewer's opinion, this result is less meaningful than the prevented fraction.

### 6.1.3 Study Design

Study 97902 is a randomized, double-blind, multinational (15 non-U.S. centers), parallel group study comparing three treatment regimens for emergency contraception each administered in two doses 12 hours apart:

- (i) one dose of 10 mg of mifepristone plus one placebo dose;
- (ii) two doses of 0.75 mg of LNG taken 12 hrs apart; and

<sup>2</sup> Dixon GW, et al. Ethinyl estradiol and conjugated estrogens as postcoital contraceptives. *JAMA* 1980;244:1336-9.

<sup>3</sup> Wilcox AJ, et al. Timing of intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Medical* 1995;333:1517-21.

(iii) one dose of 1.5 mg of LNG plus one placebo dose.

The treatment regimens were given orally during one treatment cycle, with the first dose (four tablets<sup>4</sup>: active + placebo) swallowed in the presence of a member of the study team who recorded the date and time of administration and the second dose (one tablet, either 0.75 mg levonorgestrel or placebo) taken off site 12 hours later. Women requesting emergency contraception within 120 hours of unprotected intercourse who satisfied the inclusion criteria, which included a negative pregnancy test and willingness to abstain from further acts of intercourse during that cycle, were randomly assigned to one of three treatment groups.

A follow-up visit was arranged about one week after the predicted onset of the next menstrual bleeding, and the date of the visit was written on the diary card. If the woman had normal menstruation, a pregnancy test was not done and she completed the trial. If menstruation was not normal, or had not started by the time of the follow-up visit, a pregnancy test was performed at the study site. For women with a negative test result, the investigator arranged another follow-up appointment approximately one week after the first; however, if the test was positive, the investigator did an ultrasound examination to estimate the duration of gestation and calculate the estimated date of conception (EDC). If menses had not occurred by the time of the second follow-up visit and the pregnancy test was again negative, treatment was regarded as successful. WHO provided the centers with pregnancy tests and condoms.

Clinicians, participants, and investigators were unaware of drug assignments and this double-blinding was maintained until after the final analysis. Principal investigators met before the trial to review the protocol and ensure uniform criteria for the assessment of outcomes. While the trial was in progress, the trial coordinator and other WHO staff visited trial sites. Principal investigators also monitored the staff; all but one of the centers had previously participated in multicenter trials of emergency contraception. This trial was not monitored by an external independent safety committee, because the drugs used are already registered and available for widespread use. Data quality monitoring was done in accordance with the standard operating procedures presently used by the WHO in Geneva.

**Reviewer's comment:** Two minor faults with the study design are the fact that:

- 1) Pregnancy testing was not done if, at the first follow-up visit, the subject believed she had a normal menstrual period, and
- 2) if menses had not occurred by the time of the second follow-up visit and the pregnancy test was again negative, treatment was regarded as successful.

In both of these cases there is still a small chance that the subject could be pregnant with pregnancy bleeding (threatened abortion) or a false-negative pregnancy test.

**Inclusion criteria:** women admitted to the study were required to fulfill all of the following:

- good general health
- able to give informed consent
- requesting emergency contraception within 120 hours after unprotected coitus
- negative pregnancy test

<sup>4</sup> The mifepristone group took two 5 mg mifepristone tablets + two levonorgestrel placebos; the two levonorgestrel groups took one or two 0.75 mg levonorgestrel tablets + one or no 0.75 mg levonorgestrel placebo tablet + two mifepristone placebo tablets

- with only one act of unprotected coitus during the current menstrual cycle
- willing to abstain from further acts of intercourse during that cycle or to use a condom or diaphragm if that were not possible
- have a history of regular spontaneous menstrual cycles (24-42 days)
- women who recently discontinued hormonal contraception or who had a recent abortion or delivery should have had at least one spontaneous menstrual cycle of normal length before the current cycle
- prepared to terminate the pregnancy should the treatment fail
- available for follow-up and living in the study area for at least the next six weeks
- willing and able to participate after the study had been explained

**Reviewer's comments:** The above criteria do not include any age limitation, but the age range in the single dose levonorgestrel group was from 14 to 49 and in the two dose levonorgestrel group from 14 to 52. The criterion of at least one spontaneous period since recent OC use, abortion or delivery does not assure a return to ovulation (and hence these women might not have been at risk of pregnancy); the "regular cycle" window of 24-42 days is liberal, especially at the upper end. This study included women up to 120 hours (5 days) after unprotected intercourse; previous studies stopped at 48 hours (Ho/Kwan, 1993) and 72 hours (WHO Study 98508, 1998). Subset analyses were done for the subjects who took their first dose between 0-72 hours and the limited number of subjects who took their first dose between 73-120 hrs; the Applicant is not making a claim to use single dose levonorgestrel 1.5 mg more than 72 hours after unprotected intercourse.

**Exclusion criteria:** women were not to be recruited if any of the following applied:

- currently pregnant or breastfeeding
- no pregnancy testing done
- use of hormonal methods of contraception during the current cycle
- use of Rhythm or Ovulation Method of Natural Family Planning and intercourse earlier in the same cycle
- unsure about the date of the last menstrual period
- a contraindication to the use of study drugs (adrenal pathology, steroid dependent cancer)
- intention to continue with the pregnancy in case the treatment fails

**Reviewer's comment:** The above exclusion criteria are acceptable. Women who missed taking one or more oral contraceptive pills and women using less reliable methods of contraception (rhythm or ovulation method) were excluded from the trial. The last exclusion is because one third of the women in the blinded trial would receive mifepristone 10 mg; with a potential fetal toxicity risk in the case of a pregnancy in this group, the protocol states that all women should be prepared to terminate the pregnancy (although this criterion could not be enforced).

**Study visits:**

**Visit 1:** At each trial site, it was anticipated that from 150-450 eligible women would be recruited after informed consent had been obtained. Subjects were randomly allocated to one of the three treatment

groups. Women took the first dose of four tablets (active + placebo) at the site under direct supervision and were instructed to take the second dose (one tablet) 12 hours later on their own. The subjects were given a diary chart to record vaginal spotting and bleeding, possible side effects, further acts of intercourse, if any, and the contraceptive method used.

**Visit 2 (first follow-up visit):** A follow-up visit was scheduled for approximately seven days after the expected onset of the next menstruation. If no bleeding had occurred by that time, a pregnancy test (usually on urine) with a sensitivity of detecting 25 IU/L of hCG was performed and the results recorded on the CRF.

**Visit 3 (second follow-up visit):** If the pregnancy test was negative at the first follow-up visit, a second follow-up visit was scheduled for approximately two weeks later, when another pregnancy test was performed. Most of the subjects with positive pregnancy tests had an ultrasound performed for dating of the estimated date of conception (EDC). A few of the subjects were followed up by phone, but had reliable information from an outside physician or clinic that established a conception during the cycle that the study drug was taken.

**Reviewer's comment:** There are three differences that make this study design stronger than the original WHO study 92908, which was the basis for the NDA 21-045 approval for Plan B in July 1999.

1. **Pregnancy testing was done on all subjects at time of enrollment**
2. **Administration of the first dose was directly observed at the site (as was the case in the 92908 trial); so it is clear that all the single dose levonorgestrel 1.5 mg subjects had 100% compliance.**
3. **Follow-up pregnancy testing and ultrasound for gestational dating was done for almost all (90%) of the pregnancies and questionable pregnancies.**

#### 6.1.4 Efficacy Findings

##### **Trial Centers:**

This trial was done in 15 family-planning clinics in China, India, Georgia, Hungary, Mongolia, Slovenia, Sweden, Finland, Switzerland, and the UK. The enrollment, loss to follow-up, and pregnancies in each of the 15 centers are shown for the two levonorgestrel arms in Table 2 below.

**Table 2 Centers and Enrollment**

Center	Single dose 1.5 mg Levonorgestrel		Two dose 0.75 mg Levonorgestrel	
	Enrolled (lost)	Pregnant	Enrolled (lost)	Pregnant
Beijing	100 (0)	3	97 (0)	3
Geneva	93 (7)	2	96 (3)	1
Helsinki	41 (1)	1	41 (1)	0
Hong Kong	99 (4)	1	99 (7)	1
Ljubljana	49 (0)	1	48 (0)	2
Manchester	49 (3)	0	49 (2)	0
Nanjing	149 (2)	3	149 (0)	3
New Delhi	49 (0)	3	50 (0)	2
Shanghai IPMCH	149 (3)	1	149 (1)	5
Shanghai IPPR	149 (0)	2	149 (1)	4
Stockholm	100 (1)	1	98 (4)	1
Szeged	107 (0)	0	106 (0)	0
Tbilisi	49 (0)	0	49 (0)	0
Tianjin	97 (0)	1	99 (0)	0
Ulambatar	99 (1)	1	98 (0)	2
All centers	1379 (22)	20	1377 (19)	24

Source: Applicant's Table 1 in Summary of Clinical Efficacy, pg. 6

**Baseline Demographics:**

There were no differences in baseline characteristics between the two levonorgestrel groups at admission. Women were young (mean 27 years), had a mean weight of 56 kg and about one fourth (26%) had used emergency contraception in the past. About 60% of the women had previously been pregnant, and about half (52%) requested emergency contraception because they had not used any contraception at the time of coitus. In all, 44% of women requested treatment within 24 hours, 73% within 48 hours, 89% within 72 hours and 96% within 96 hours. A total of 303 (11%) of the 2,756 subjects who were administered levonorgestrel were > 72 hours from the time of unprotected intercourse. Relating to ethnicity, 54% of the participants were Chinese, 12% were non-Chinese Asian or Black, and 34% were Caucasian in each treatment group. Distribution of the day of intercourse relative to ovulation was similar between the groups. Approximately just as many women had intercourse before the estimated day of ovulation as after ovulation.

**Reviewer comment:** Another way of looking at the timing of the first dose are the following percentages of women taking the drug within each 24-hour interval: 0-24 hr (44%), 25-48 hr (29%), 49-72 hr (16%), 73-96 hr (7%), and 97-120 hr (4%) post unprotected intercourse.

**Enrollment:**

1,379 women were randomized in the levonorgestrel single dose group (designated hereafter group 1), and 1,377 were randomized in the levonorgestrel two dose group (designated hereafter group 2). Twenty-two women were lost to follow-up in group 1, and 19 in group 2; one woman had the index episode of

b(4)

intercourse after missed menses in group 1, and two in group 2. These subjects were considered as non-evaluable. Thus 1,356 women completed the study in each group. These women were included in the Study Population, hereafter called the full ITT (Intent-To-Treat) population. The restricted ITT population was defined as a subpopulation of the full ITT set, excluding all major protocol violations. In the two levonorgestrel groups, there were 156 protocol violations recorded for 144 women, since there were 12 women having more than one violation. There were 68 protocol violations in 63 women with group 1: among them 10 had a delay of initiating treatment more than 120 hours, and four women had a cycle length of other than 24-42 days, 23 used rhythm methods in the current (treatment) cycle, and 31 had further acts of unprotected intercourse. In group 2, 88 protocol violations were recorded in 81 women: 13 of them took the treatment more than 120 hours after unprotected intercourse, and eight women's cycle length was not in accordance with the protocol's inclusion criterion, 37 used rhythm methods in the current cycle, and 30 had further acts of unprotected intercourse. The restricted ITT population consisted of 1,293 women in group 1, and 1,275 women in group 2. The PP (Per Protocol) population was defined as the subpopulation of restricted ITT population excluding women with treatment non-compliance. The study was conducted according to the protocol in 1,276 women in group 1 and 1,258 women in group 2. The efficacy analysis was performed for all the sets, but this review will focus on the full ITT set and the restricted ITT population. Table 3 below summarizes the different patient populations.

**Table 3 Patient Populations**

Patient Populations	Group 1 Single dose	Group 2 Two dose	MO comment
Enrolled initially	1,379	1,377	All subjects given one dose of drug
Lost or non-evaluable	23	21	19 lost + 2 were non-evaluable
Full ITT (completed study)	1,356	1,356	All subjects who completed study
Protocol Violations	68	88	12 women had 2 violations
>120 hrs post coitus	(10)	(13)	
Abnormal cycle length	(04)	(08)	
Rhythm method used	(23)	(37)	
Further acts of coitus	(31)	(30)	
Restricted ITT	1,293	1,275	Full ITT minus 156 protocol violators
Treatment non-compliance	(17)	(17)	
Per Protocol Population (PP)	1,276	1,258	Restricted ITT minus treatment non-compliers

Source: Reviewer table based on Applicant's data and definitions of patient populations

**Reviewer's comment:** This reviewer agrees with the Applicant's definition of the different patient populations. It does seem unnecessary to remove 17 patients from the single dose levonorgestrel group Per Protocol population for treatment non-compliance because all of these subjects were compliant with their active treatment dose; in terms of efficacy, it is irrelevant whether they did not take their second dose on time or not at all. In any case, the trial had a large number of subjects in each arm and in both of the two Per Protocol groups, which are best for evaluating the perfect-use efficacy of the products, there were well over 1,250 subjects.

### **Efficacy Findings:**

#### **Single dose levonorgestrel pregnancies:**

There were 20 pregnancies in the full ITT population of women who took single dose levonorgestrel. The CRFs for these 20 women were carefully analyzed by the FDA clinical reviewer. There are certain key factors that potentially help explain some of the failures in these 20 women. They are as follows:

1. **Time of first dose:** four of the women took their treatment at > 72 hours, namely 88, 108, 109, and 110 hours after unprotected intercourse. Further discussion of the importance of starting treatment as soon as possible is found later in this Section 6.1.4.
2. **Sex after treatment exposure:** seven women had further acts of intercourse (from one to three acts) during the treatment cycle - two women without additional birth control and five women (with a total of ten acts) with additional non-hormonal birth control.
3. **Uncertain conception date:** two women (060-E and 135-R) did not have ultrasounds:
  - Subject 060-E had unprotected sex on Day 7 and took her treatment 69 hours later, but had two additional acts of unprotected intercourse and became pregnant probably because of those subsequent acts.
  - Subject 135-R had a condom failure on Day 20 of her usual 30 day cycle and took her treatment 11 hours later; her urine pregnancy test was positive on Day 36, but an ultrasound was not performed, so the date of conception cannot be confirmed. She may have been pregnant (fertilized egg) at the time she was treated on Day 20-21 of her cycle.
4. **Pregnancy prior to treatment:** Subject 103-T had a condom failure on Day 25 of her 30 day cycle and took her treatment 20 hours later; an ultrasound showed an estimated date of conception on Day 17 of her normal 30 day cycle, so she may have already been pregnant, but would have had a negative pregnancy test when she took her treatment on Day 25.
5. **Ethnic origin:** ten (50%) of the 20 pregnant women were Chinese. However, 54% of the women enrolled were Chinese. Further discussion of ethnic origin is found later in this Section

#### **Efficacy results in the different patient populations:**

Among all the women included in the full ITT population, 20 of 1,356 (1.5%) in the levonorgestrel 1.5 mg x 1 group and 24 of 1,356 (1.8%) in the levonorgestrel 0.75 mg x 2 group were found to be pregnant. Among women receiving the levonorgestrel single dose regimen, 81.9% of the expected pregnancies were prevented (95% CI: 72.1% to 88.9%). 77.3% of expected pregnancies were prevented among those taking the two dose 0.75 mg levonorgestrel (95% CI: 66.3% to 85.5%). The results for the full ITT population are shown in Table 4 below.

**Table 4 Full ITT Population Pregnancy Rate and Prevented Fraction**

	N	Observed Pregnancies			Expected Pregnancies		
		n	Rate (%)	95% C.I.	n	PF* (%)	95% C.I.
Levonorgestrel 1.5 mg * 1	1356	20	1.47	(0.90, 2.27)	110.5		
Levonorgestrel 0.75 mg * 2	1356	24	1.77	(1.14, 2.62)	105.8		

Source: Table 11-12, page 51/116 of Clinical Study Report dated February 24, 2003

\* PF = Prevented Fraction =  $1.0 - (\text{Observed pregnancies} / \text{Expected pregnancies})$

In the restricted ITT population, there were 18 pregnancies (1.4%) among 1,293 women in the single dose levonorgestrel group and 20 (1.6%) among 1,275 women in the two dose levonorgestrel group. The prevented fractions were 82.9% (CI: 73.0% to 89.9%) in the single dose levonorgestrel regimen and 80.1% (CI: 69.3% to 87.8%) in the two dose levonorgestrel regimen.

The per protocol (PP) population showed very similar results with a pregnancy rate of 1.4% (95% CI: 0.83% to 2.22%) in the single dose levonorgestrel group and 1.6% (95% CI: 0.97% to 2.44%) in the two dose levonorgestrel group. Prevented fractions were 82.7% (CI: 72.6% to 89.7%) for the single dose levonorgestrel regimen and 79.8% (CI: 68.7% to 87.6%) for the two dose levonorgestrel regimen.

There was no statistically significant difference between the pregnancy rates for the two levonorgestrel groups ( $p > 0.6$ ) when all three patient populations were combined and analyzed by the Applicant.

**Reviewer comment:** There were three women who were excluded from the efficacy analysis because of requesting emergency contraception after the expected date of menses. None were pregnant. Unreported pregnancies among the women lost to follow-up could bias the results, but these 41 women (22 from the single dose group; 19 from the two dose group) represented only 1.5% of the 2,756 women enrolled in the two levonorgestrel arms. Even with the unlikely scenario that all of the 41 women were pregnant, the pregnancy prevented fractions would be 61.8% and 55.5%, respectively, for the single dose and two dose groups.

**Table 5 Summary Pregnancy Rates and Prevented Fractions**

Patient Population	Pregnancy Rate (Percent)		Pregnancy Prevented Fraction (Percent)	
	Group 1 (single dose)	Group 2 (2 dose)	Group 1 (single dose)	Group 2 (2 dose)
Full ITT	1.47	1.77	81.9	77.3
Restricted ITT	1.39	1.57	82.9	80.1
Per Protocol	1.41	1.59	82.7	79.8

Source: Reviewer's summary table; the 95% confidence intervals are found in the preceding review text.

The crude relative risk (RR) of pregnancy for single dose levonorgestrel compared with two dose levonorgestrel was 0.83 (CI: 0.46-1.50) in the full ITT set and 0.89 (CI: 0.47-1.67) in both the restricted ITT and PP populations. The 95% confidence limits around the relative risk include 1, which indicates that the two levonorgestrel regimens had the same effectiveness when judged by this criterion.

The adjusted RR of pregnancy for single dose 1.5 mg levonorgestrel compared with two dose 0.75 mg levonorgestrel, adjusted for the number of expected pregnancies in each group, was 0.80 (0.42-1.51) in

the full ITT population and 0.85 (CI: 0.43-1.70) in the restricted ITT and in the PP populations. These results were very similar to the crude results.

**Reviewer's comment:** All of the above parameters (pregnancy rates, pregnancy prevented fractions, and crude and adjusted relative risk of pregnancy) for the three patient populations demonstrate that there is no significant difference between the single dose and two dose levonorgestrel regimens when analyzing the data for the women who started treatment within 120 hours of unprotected intercourse. This reviewer agrees with the Applicant's data, analysis and calculations. No claims of efficacy superior to Plan B are made by the Applicant. Based on the overall comparative results for pregnancy prevention effectiveness, the single dose levonorgestrel 1.5 mg should be approved.

**Efficacy Results from the Three Populations Starting Treatment Within 0-72 Hours**

The Applicant is seeking approval for single dose levonorgestrel for emergency contraception only for women up to 72 hours after unprotected intercourse. This subset of women in the trial was analyzed by the Applicant for all the same parameters as used for the entire set of women. The 0-72 hour subset shows that compared to the entire trial population the pregnancy rates are slightly lower [range 0.05 to 0.18% lower] and the pregnancy prevented fractions are higher [range 1.1- 2.4% higher]. In the full ITT 0-72 hour population there were 2,381 women, 331 fewer than in the 0-120 hour full ITT set. In the Restricted ITT 0-72 hour population there were 2,272 women, 296 fewer than the 0-120 hour set. In the Per Protocol 0-72 hour population there were 2,242 women, 292 fewer than in the 0-120 hour set. Table 6 shows the pregnancy rates and pregnancy prevented fractions for the three patient populations for the two treatment groups.

**Table 6 Summary Pregnancy Rates and Prevented Fractions (0-72 hour subset)**

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

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

**Reviewer's comment:** The results above and the Applicant's analyses for crude relative risk of pregnancy, and efficacy in Chinese and non-Chinese women, and by age group do not differ significantly from the results shown in Table 5 for the entire trial population of women who started treatment within 120 hours of unprotected intercourse. Three trends are noticeable, but not statistically significant, in the 0-72 hour subset of women:

1. The overall pregnancy rates are slightly lower in all three patient populations compared to the results for the 0-120 hour group.
2. The overall pregnancy prevented fractions are slightly higher in all three patient populations compared to the results for the 0-120 hour group.
3. The overall results in the 0-72 hour subset are slightly better in the single dose levonorgestrel group compared to the two dose levonorgestrel group.

**Efficacy Results from Chinese and non-Chinese Populations:**

For Chinese women compared to non-Chinese women, data that were reviewed for the approval of NDA 21-045 (two dose levonorgestrel Plan B) showed that the pregnancy rate from the large WHO 92908 study was approximately doubled [1.8% vs. 0.8%]. This finding was also addressed in the current NDA submission using data from the equally large WHO study 97902.

The pregnancy rate among Chinese women in the full ITT population in group 1 was 1.50% (95% CI 0.75% to 2.67%) and among non-Chinese women it was 1.44% (95% CI 0.66% to 2.72%). In the same population the pregnancy rate in group 2 among Chinese women was 2.19% (95% CI 1.25% to 3.53%), while among non-Chinese women it was 1.28% (95% CI 0.56% to 2.51%). Prevented fractions for Chinese and non-Chinese women, respectively, were 80.9% (95% CI 66% to 90%) and 83.0% (95% CI 68 to 92) in group 1, and 70.4% (95% CI 52% to 83%) and 84.6% (95% CI 70 to 93) in group 2, for Chinese and non-Chinese women, respectively. Chinese women also became pregnant more frequently than non-Chinese in the two other analyzed populations. The difference between Chinese and non-Chinese women, however, was not statistically significant ( $p > 0.2$  for all three analyzed populations). Of the 1,465 Chinese women in the two treatment groups combined, 27 (1.84%) became pregnant. Of the 1,247 corresponding combined women in the non-Chinese centers, 17 (1.36%) became pregnant. See Table 7 and Table 8 below.

**Table 7 Full ITT Population, Ethnic group: Chinese**

Group	N	Observed Pregnancies				Expected Pregnancies			
		#	Rate	95%LL	95%UL	#	Prevented Fraction	95%LL	95%UL
Levonorgestrel 1 dose	733	11	1.50	0.7515	2.6692	57.6	80.89	65.80	90.46
levonorgestrel 2 dose	732	16	2.19	1.2544	3.5254	54.0	70.36	51.86	83.06
<b>All groups</b>	<b>1465</b>	<b>27</b>	<b>1.84</b>			<b>111.6</b>	<b>75.62</b>		

Source: Applicant Summary of Clinical Efficacy, pg. 12.

**Table 8 Full ITT Population, Ethnic group: Non-Chinese**

Group	N	Observed Pregnancies				Expected Pregnancies			
		#	Rate	95%LL	95%UL	#	Prevented Fraction	95%LL	95%UL
levonorgestrel 1 dose	623	9	1.44	0.6626	2.7246	52.9	83.00	67.73	92.23
levonorgestrel 2 dose	624	8	1.28	0.5551	2.5105	51.9	84.58	69.61	93.34
<b>All groups</b>	<b>1247</b>	<b>17</b>	<b>1.36</b>			<b>104.8</b>	<b>83.79</b>		

Source: Applicant Summary of Clinical Efficacy, pg. 12.

The pregnancy rate among Chinese women in the per protocol population in group 1 was 1.44%, and among non-Chinese women it was 1.37%. In the same PP population the pregnancy rate in group 2 among Chinese subjects was 1.94%, while among non-Chinese subjects it was 1.19%. Prevented fractions for Chinese and non-Chinese women, respectively, were 81.52% and 83.96% in group 1, and 73.49% and 85.92% in group 2. In the two levonorgestrel groups combined, out of the 1,364 Chinese women, who completed the follow-up, 23 (1.7%) became pregnant. Of the 1,170 corresponding non-Chinese women combined, 15 (1.3%) became pregnant. See Table 9 and Table 10 below.

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**Table 9 PP Population, Ethnic group: Chinese**

Group	N	Observed Pregnancies				Expected Pregnancies			
		#	Rate	95%LL	95%UL	#	PF	95%LL	95%UL
levonorgestrel 1dose	693	10	1.44	0.6941	2.6377	54.1	81.52	66.01	91.14
levonorgestrel 2doses	671	13	1.94	0.0355	3.2902	49.0	73.49	54.67	85.89
All groups	1364	23	1.69			103.1	77.51		

Source: Applicant's Summary of Clinical Efficacy, pg. 13.

**Table 10 PP Population, Ethnic group: Non-Chinese**

Group	N	Observed Pregnancies				Expected Pregnancies			
		#	Rate	95%LL	95%UL	#	PF	95%LL	95%UL
levonorgestrel 1 dose	583	8	1.37	0.5942	2.6858	49.9	83.96	68.39	93.07
levonorgestrel 2 dose	587	7	1.19	0.4808	2.4415	49.7	85.92	70.99	94.34
All groups	1170	15	1.28			99.6	84.94		

Source: Applicant's Summary of Clinical Efficacy, pg. 13.

**Reviewer's comment:** In the original NDA for Plan B (two dose levonorgestrel) there was a noticeable difference in the pregnancy rates and prevented fractions between the Chinese and non-Chinese populations. The label for Plan B states:

*No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both Plan B™ and the Yuzpe regimen (another form of emergency contraception consisting of two doses of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown.*

The Applicant has proposed that the label for the single dose product remain the same as for Plan B. This reviewer agrees with the proposal. WHO Study 97902 does not, however, demonstrate a statistically significant decrease in contraceptive efficacy for Chinese women comparing the single and two dose regimens in the three patient populations for both the entire trial set and the 0-72 hour subset of women.

**Efficacy Results from Different Age Populations:**

Table 11 presents the pregnancy rate and, in the highlighted area, the prevented fraction in the full ITT population using two age groups: 35 years of age or less and > 35 years of age. The FDA clinical reviewer and statistical reviewer concur with the Applicant's results.

More than 85% of the women in Study 97902 were 35 years of age or less. There were 40 pregnancies observed in this age group, 19 (1.6%) in the single dose levonorgestrel group and 21 (1.8%) in the two dose levonorgestrel group. There were 185 pregnancies expected if no contraceptive measures were taken; 94 in the single dose levonorgestrel group and 91 in the two dose levonorgestrel group. So, the percentage of pregnancies that was prevented was 79.7% (95% CI from 68.3% to 87.8%) for the LNG 1.5 mg x 1 regimen and 76.8% (95% CI from 64.6% to 85.6%) for the LNG 0.75 mg x 2 regimen.

Approximately 15% of the women were 36 years of age or older. There were 4 pregnancies observed in this age group; 1 (0.5%) in the single dose levonorgestrel group and 3 (1.5%) in the two dose levonorgestrel group. There were 32 pregnancies expected if no contraceptive measures were taken, 17 in the single dose levonorgestrel group and 15 in the two dose levonorgestrel group. For the single dose

levonorgestrel regimen, the percentage of pregnancies that was prevented was 94.1% (95% CI from 67.1% to 99.9%) for and 80.4% (95% CI from 42.7% to 96.0%) for the two dose levonorgestrel regimen.

**Table 11 Efficacy Results by Age Groups (Full ITT Population)**

	N	Observed Pregnancies			Expected Pregnancies		
		n	Rate (%)	95% C.I.	n	PF* (%)	95% C.I.
<b>35 Years of Age or Less</b>							
Levonorgestrel 1.5 mg × 1	1166	19	1.63	(0.98, 2.53)	93.6		
Levonorgestrel 0.75 mg × 2	1151	21	1.82	(1.13, 2.78)	90.6		
<b>36 Years of Age or More</b>							
Levonorgestrel 1.5 mg × 1	190	1	0.53	(0.01, 2.90)	16.9		
Levonorgestrel 0.75 mg × 2	205	3	1.46	(0.30, 4.22)	15.3		

Source: Two tables for Full ITT Population in Section 1.1.1 on page 6 of submission dated 6-29-06.

\* PF = Prevented Fraction =  $1.0 - (\text{Observed pregnancies} / \text{Expected pregnancies})$

**Reviewer's comment:** Although the single dose levonorgestrel appears to be more effective\* than the two dose regimen, there is not a statistically significant difference between these two regimens in either the 0-120 hour analysis or the 0-72 hour subset of women. Concerning the two age groups using the single dose, the better results in the older age group are expected as fecundity decreases with age, so contraceptive effectiveness is expected to increase. Single dose levonorgestrel should be approved for both age groups.

\*Another explanation is that the calculations for the expected number of pregnancies are overestimated (because of decreased fecundity with increasing age) and that the contraceptive efficacy is actually not more effective in the older age group. However, no adjustment was made by the Applicant in the calculation of expected pregnancy rates based on age.

**Efficacy Results by Timing of First Dose:**

The Applicant's analysis stratified by time interval between intercourse and treatment showed that shorter intervals were associated with lower pregnancy rates in both levonorgestrel groups. For the two levonorgestrel arms combined in the full ITT population, the 126 women who were treated after 96 hours had a 4.76% pregnancy rate (6/126) compared to the 1.48% rate (38/2,569) in the women who were treated within 96 hours. The difference was significant in each of the three patient population efficacy sets (full ITT, p=0.030; restricted ITT, p=0.049; Per Protocol, p=0.047).

For the two levonorgestrel arms combined, women who were treated after 72 hours had higher pregnancy rates than women who were treated within 72 hours. In the full ITT population for the single dose levonorgestrel group, the pregnancy rates on days 1, 2, 3, 4 and 5 were 1.6% (10/622), 0.5% (2/377), 2.0% (4/199), 1.1% (1/87), and 4.8% (3/63). The results were similar for the two-dose levonorgestrel regimen. A significant difference was found, however, only in efficacy between women starting the treatment within four days and after four days of unprotected intercourse.

In the previous WHO Study 92908, a noticeable increasing trend in failure rates with delay in treatment was found. This trend of declining efficacy with time elapsed before starting treatment was not as clearly demonstrated by the data submitted from the WHO 97902 study. Despite this the Applicant believes it is important to emphasize taking the treatment as soon as possible, since it is an emergency measure for contraception.

**Reviewer's comment:** This reviewer agrees with the Applicant's proposal that the single dose levonorgestrel should be labeled to be taken within the first 72 hours after intercourse. In the full ITT population for the single dose, the pregnancy rate was 1.34% (16/1,198) if taken within the first 72 hours and two-fold higher at 2.67% (4/150) if taken within the 73-120 hour range. Because the primary mechanism of action is by either blocking or delaying ovulation, it makes sense physiologically that the sooner the treatment is taken, the greater the chances for preventing a pregnancy.

**Further Acts of Unprotected Intercourse:**

The association between efficacy and further acts of unprotected intercourse was also evaluated in the study analysis. Having further acts of intercourse between treatment and the next expected menstruation resulted in higher pregnancy rates in the pivotal study: in the levonorgestrel groups of the full ITT population a total of 2,651 women reported not having had any further intercourse, while 61 women (2.3%) reported at least one further act of intercourse prior to their next menses.

Among women without further acts of intercourse, the pregnancy rate with single dose levonorgestrel was 1.36% (95% CI 0.80% to 2.13%), while with two dose levonorgestrel it was 1.66% (95% CI 1.04% to 2.50%). Among women with further acts of intercourse, the pregnancy rates were 6.45% (95% CI 0.79% to 21.42%), and 6.67% (95% CI 0.81% to 22.07%), for the single dose and two dose groups, respectively. Pregnancy rates were clearly lower if further acts of protected or unprotected intercourse had not occurred.

**Reviewer's comment:** Although only 2.3% of the women taking levonorgestrel in the trial reported having further acts of intercourse prior to their next menses, 35% (seven) of the 20 pregnant women taking the single dose levonorgestrel reported further acts of intercourse. Of these seven women, two reportedly did not use any birth control method with the at least one of the additional acts of intercourse. Labeling for the approved product should clearly reflect this finding and caution that further acts of intercourse will increase the chances of a pregnancy and that it is best to avoid intercourse until after the next spontaneous menstrual period.

**Efficacy Results from the Nigerian Trial:**

The findings from the publication of the blinded, randomized Nigerian study comparing single dose and two dose levonorgestrel for emergency contraception with 1,118 evaluable women were incorporated into the Applicant's Summary of Clinical Findings. The protocol for this study was very similar to the WHO Study except that all the women were within 72 hours of unprotected intercourse and there was not a third treatment arm. Eleven pregnancies (0.98% overall pregnancy rate) were reported (four in the single dose group; seven in the two dose group). The crude relative risk of pregnancies was similar in the two groups; for single dose compared to two dose treatment the crude RR = 0.71 (95% CI 0.32-1.55;  $p > 0.05$ ). 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 with delay in starting treatment after unprotected intercourse and if further acts of unprotected intercourse took place after treatment. Table 12 summarizes the results for the ITT population.

**Table 12 Efficacy Results in ITT Population- Nigerian Trial**

Group	N	Observed Pregnancies				Expected Pregnancies			
		#	Rate	95%LL	95%UL	#	Prevented Fraction	95%LL	95%UL
levonorgestrel 1 dose	573	4	0.69	0.02	1.38	57.1	92.99	81.25	97.38
levonorgestrel 2 dose	545	7	1.28	0.34	2.20	53.1	86.80	72.07	93.77

Source: Composite data from publication of Nigerian trial results.

**Reviewer's comment:** The findings here are based entirely on the publication of the results from the large, blinded, comparative Nigerian study. The original datasets and CRFs were not submitted or required as part of the NDA application. The trial population is presumably close to 100% African. In any case, the results from this study showed the following:

1. Single dose levonorgestrel is at least as effective for preventing a pregnancy as the two dose regimen.
2. The earlier either levonorgestrel regimen was started following unprotected intercourse, the greater the efficacy.
3. Pregnancy rates increased if further acts of intercourse took place after treatment and prior to the next menstrual period.

### 6.1.5 Clinical Microbiology

No clinical microbiology was required for this NDA submission, as the drug is administered orally.

### 6.1.6 Efficacy Conclusions

The two levonorgestrel regimens are highly effective for emergency contraception. The WHO 97902 study showed that in the full ITT population of over 2,700 women the single dose 1.5 mg levonorgestrel regimen had a slightly better, but not statistically significantly different, effectiveness (82% of expected pregnancies prevented) as compared to the two dose 0.75 mg levonorgestrel (77% of pregnancies prevented). A trend towards lower efficacy with a longer delay in taking the levonorgestrel drug after unprotected intercourse was evident when considering the pregnancy rates for two time intervals (from 0 to 72 hours, and from 73 to 120 hours).

The Arowojolu et al. study in Nigeria<sup>5</sup> is supportive of the effectiveness of both levonorgestrel regimens taken within 72 hours of unprotected intercourse. It also supports the first three comments that are listed below.

Concerning efficacy it is important to emphasize the following:

1. Take the treatment as soon as possible for emergency contraception after unprotected intercourse, and within 72 hours of the event.
2. Further acts of intercourse before the onset of the next menstrual period should be strongly discouraged, as this will increase the chances of an unplanned pregnancy.
3. Treatment is effective for women of all reproductive ages.

<sup>5</sup> *Contraception* 2002;66:269-273.

4. Effectiveness in Chinese women may be slightly, but not statistically significantly, lower compared to non-Chinese women.
5. Treatment does not protect against HIV and other sexually transmitted infections.
6. Lastly, treatment is for emergency contraception and not for routine contraception.

Single dose 1.5 mg levonorgestrel should be approved for emergency contraception up to 72 hours after known or suspected contraceptive failure or unprotected intercourse in women of all reproductive ages. It is also this reviewer's opinion that the product should go directly over-the-counter (OTC) because it fulfills the regulatory criteria for such a use. The efficacy and safety for single dose 1.5 mg levonorgestrel appear to be the same as for two dose 0.75 mg levonorgestrel (Plan B). There is no need for a learned intermediary and compliance for the single dose regimen should be much better than for the two dose levonorgestrel regimen (12 hour dosing is awkward because of potential night-time dosing).

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

In the WHO Study 97902, all women who had received at least one dose of study medication were included in the safety analysis. All women took the first dose of study medication under direct observation; thus, 1,379 women were included in the safety analysis in the levonorgestrel single dose group, and 1,377 women in the levonorgestrel two dose group.

Participants were asked to keep a diary of side-effects in the week after the treatment, and to record spotting or bleeding, acts of intercourse and whether a condom was used, until the next menses or the follow-up visit, whichever came first. Expected side effects were listed on the diary card to be checked if they occurred; additional comments were also allowed to be written on the diary card and CRFs. No incentives were given, and the trial drugs were supplied free of charge to participants.

#### 7.1.1 Deaths

There were no deaths in the WHO or Nigerian trials.

#### 7.1.2 Other Serious Adverse Events

In women taking levonorgestrel, there were three reports of serious adverse events (AEs) during the study. In the levonorgestrel single dose group two serious adverse events were reported:

1. Subject 1340/0013-R, age 28, developed a corpus luteum cyst, was hospitalized eight days after taking the levonorgestrel and had a laparoscopy for a ruptured cyst and recovered.
2. Subject 0001/0213-C had an acute appendicitis and was hospitalized, operated on, and recovered.

In the levonorgestrel two dose group, Subject 0001/0009-W, age 26, had an ectopic pregnancy diagnosed by the absence of an amniotic sac and an increasing serum hCG. A complete post-operative recovery was reported.

**Reviewer's comment:** These three events are classified as serious because the women were hospitalized. The investigators assessed that the appendicitis and ruptured corpus luteum cyst were not due to the levonorgestrel. This reviewer agrees.

**There was one ectopic pregnancy and 44 documented pregnancies in women taking levonorgestrel (single or two dose) in the trial. 1-2% of all pregnancies are expected to be**

**ectopic. The occurrence rate of one ectopic out of 44 pregnancies is 2.2%, slightly above the expected range. If the findings from the Nigerian trial (11 pregnancies with no ectopic pregnancies) are added to the WHO Study data, the incidence drops to 1.8% (1/55). These findings do not raise a safety issue and there is no signal that women who use levonorgestrel for emergency contraception have an increased absolute rate of ectopic pregnancy.**

**In March 2004, this reviewer's extensive review of the safety of two dose levonorgestrel (Plan B) carefully evaluated serious adverse events and ectopic pregnancies and found no safety concerns.**

### 7.1.3 Dropouts and Other Significant Adverse Events

The trial was for a one-time use of an active treatment to prevent a pregnancy. There were 41 women who took at least one dose of levonorgestrel and were lost to follow-up, but there were no women who were documented to have dropped out because of an adverse event. For the common adverse events experienced by the women in the trial, see Section 7.1.5 below.

The overall dropout (no follow-up) rate was 1.5%. At the 4 European centers the dropout rate ranged from 1.6 to 5.0%; the 4 Eastern European centers ranged from 0 to 0.3%; the 6 Chinese centers ranged from 0 to 6.4%, and the New Delhi center had a 3.4% dropout rate. Total enrollment per center for the three treatment arms ranged from 147 to 447 women for the three treatment arms.

**Reviewer's comment: The dropout rates did not demonstrate any noticeable regional or cultural differences.**

#### 7.1.3.1 Overall profile of dropouts

These women were normal healthy women; no obvious profile associated with loss to follow-up was noted.

#### 7.1.3.2 Adverse events associated with dropouts

Because the trial was for a single-use treatment, there is no accurate accounting of why a small number of women were lost to follow-up. It may have been due to adverse events or for other reasons; these women simply missed the one scheduled follow-up clinic visit and the study sites were unable to contact the women for further information.

#### 7.1.3.3 Other significant adverse events

There were no other significant adverse events reported in the WHO trial using a one-time treatment for emergency contraception. Although repeat use of levonorgestrel for either routine post-coital or emergency contraception has been shown to be safe, this study did not enroll women for repeat use of emergency contraception within the trial.

### 7.1.4 Other Search Strategies

The peer-reviewed medical literature on emergency contraception using levonorgestrel was searched for safety and efficacy data. The 12<sup>th</sup> annual meeting of the American Society for Emergency Contraception was attended by this reviewer on October 6, 2006 in New York City to learn the latest updates and issues. The annual report for Plan B and the most recent AERS reports for Plan B were reviewed as well as the PSUR from Gedeon Richter.

## 7.1.5 Common Adverse Events

### 7.1.5.1 Eliciting adverse events data in the development program

Two-dose 0.75 mg levonorgestrel was approved in July 1999 and has an excellent safety profile. It was deemed sufficient by the Division that for this NDA the Applicant submit the original data sets from the WHO trial comparing single dose and two dose levonorgestrel for emergency contraception.

**Trial AE data collection:** A checklist of adverse events and menstrual events was provided on the subject's diary card. The checklist was to be completed for seven days after enrollment. The list included nausea, vomiting, diarrhea, fatigue/weakness, dizziness, headache, breast tenderness, lower abdominal pain, vaginal bleeding and spotting. The information from the diary card was transferred to the CFR during the first follow-up visit. Additional comments were allowed to be written on the diary card and CRFs. The checklist of adverse events was prepared because the adverse events on it were thought to be expected during the course of the study and were regarded as likely to be related to the study medication in most instances.

Other complaints and illnesses were recorded on Adverse Event Report forms. If the adverse event was to be considered as serious, a Serious Adverse Event Report Form was filled in.

### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse event data was first recorded on the subjects' daily diaries and trial AE Report Forms. This data was then entered simultaneously by two operators into two independent databases. Next these adverse events were coded using MedDRA terminology for medical text by the Clinical Drug Safety Unit of Gedeon Richter Ltd.

### 7.1.5.3 Incidence of common adverse events

**Common Adverse Events:** The occurrence of adverse events was low and varied between the study centers. There were a total number of 4,226 adverse events (2,120 in the levonorgestrel one dose group, and 2,106 in the levonorgestrel two dose group) observed during the study. A total of 1,388 women reported at least one AE (695 in the levonorgestrel one dose group, and 693 in the levonorgestrel two dose group).

Women tolerated the study preparations well. The most common adverse events (range 31-10%) included vaginal bleeding, nausea, lower abdominal pain, and fatigue, headache and dizziness. Vomiting was negligible in both treatment groups, about 1.4% of women reporting it in each group.

While bleeding disturbances were reported by 31% of subjects, delay of next menses more than seven days from the expected menses occurred in only 4.5% of subjects in each of the two levonorgestrel groups.

**Bleeding data:** More than half of the women in the two levonorgestrel groups had menses within two days of the expected time. The characteristics of bleeding were similar compared with normal menstruation in over 75% of the women. Table 13 and Table 14 show findings for the duration, onset, and comparative amount of bleeding for the two levonorgestrel regimens.

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**Table 13 Duration and Onset of Next Menses**

Menstrual Data	Levonorgestrel One dose			Levonorgestrel Two dose		
	N	Mean	SD	N	Mean	SD
Duration of bleeding (days)	1331	5.1	1.6	1329	5.2	1.7
Onset of next menses: [Deviation from expected time (days)]	1333	-1.1	5.9	1330	-1.2	6.1
		n	%		n	%
Within 5 days	1336	1039	77.8	1332	985	73.9
Within 2 days	1336	746	55.8	1332	702	52.7
Earlier than 2 days	1336	386	28.9	1332	410	30.8
Later than 2 days	1336	204	15.3	1332	220	16.5
*Later than 7 days	1359	61	4.5	1353	61	4.5

Source: modified from Applicant's Table 9 in Summary of Clinical Safety, pg. 17-18.

\*Source: Applicant's Table 7 in Summary of Clinical Safety, pg. 15.

**Table 14 Comparative Bleeding**

Compared with Subject's normal menstruation	Levonorgestrel One dose			Levonorgestrel Two dose		
	N	n	%	N	n	%
Less	1336	142	10.6	1332	149	11.2
Similar	1336	1031	77.2	1332	1015	76.2
More	1336	145	10.9	1332	149	11.2
Much more	1336	14	1.0	1332	13	1.0

Source: modified from Applicant Table 9 in Summary of Clinical Safety, pg. 17-18.

**Reviewer's comment:** The bleeding profiles here for the two levonorgestrel regimens are virtually the same. Noteworthy are the findings that 56% of the single dose women had their next menses within two days of the expected time (78% within 5 days), only 4.5% were later than seven days after expected, and 88% of the women had bleeding similar to, or less than, their normal menses. This profile is generally acceptable and does not raise any safety concerns.

In the Nigerian trial there were two findings concerning the bleeding profiles that are different from the WHO Study. 15.5% of women taking single dose levonorgestrel reported "heavy menses", compared to 10.5% of the women taking two dose levonorgestrel. 19.9% in the single dose group had the onset of expected menses > 7 days compared to 14.9% in the two dose group (this finding is considerably more than the 4.5% incidence seen in the two groups in the WHO Study).

As noted in the proposed label

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#### 7.1.5.4 Common adverse event tables

The common adverse events are in fact the drug-related AEs. Refer to the next section and Table 15 for further information.

#### 7.1.5.5 Identifying common and drug-related adverse events

The Table 15 below lists the ten most common adverse events that were determined in advance to be expected during the course of the clinical trial and were regarded as likely to be related to the study drug. There was no statistically significant difference in the incidence of adverse events between the two levonorgestrel groups.

Table 15 Most Common Drug-related AEs in descending order

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

\*Rounded to the nearest whole number in most cases

Source: Reviewer's table with data from Applicant's Summary of Clinical Safety

#### 7.1.5.6 Additional analyses and explorations

In the Applicant's Summary of Clinical Safety, additional analyses were made for the common adverse events within the first seven days after treatment, and then stratified by days, and for all adverse events that were reported at least once. The entire set of adverse events was also classified according to MedDRA system-organ classes.

**Reviewer's comment:** These additional analyses do not raise any new safety concerns. The most common side effects in subjects taking levonorgestrel are the ones that are well-known and discussed in Section 7.1.5 above.

#### 7.1.6 Less Common Adverse Events

Other than the ten most common adverse events listed in Table 15, there were no adverse events that were reported by > 1% of the trial population.

## 7.1.7 Laboratory Findings

### 7.1.7.1 Overview of laboratory testing in the development program

Other than pregnancy testing, no additional laboratory investigations were conducted for the purposes of the study. Results of safety-related laboratory tests were not collected during the course of the study. Urinary pregnancy testing ( $\beta$ -hCG; sensitivity 25 IU/l) had to be done before actual enrollment. This was required to exclude an already existing pregnancy.

If the woman had not resumed menstruation by the time of the first follow up visit, a urinary hCG (or serum hCG) had to be determined. The same procedure was carried out if menstruation had not started by the time of the second follow up visit.

**Reviewer's comment:** The very limited laboratory tests is acceptable because of the well-established safety profile of levonorgestrel for emergency contraception and because the trial was for a one-time use of the study products.

### 7.1.7.2 Additional analyses and explorations

There were none.

### 7.1.7.3 Special assessments

There were none.

## 7.1.8 Vital Signs

Height and weight were recorded on the admission form for the first visit. Otherwise, no vital signs were taken or indicated because the trial treatment is a one-time treatment for an emergency indication. Chronic daily administration of 1.5 mg levonorgestrel is not indicated or recommended.

## 7.1.9 Electrocardiograms (ECGs)

No ECGs were taken or indicated.

## 7.1.10 Immunogenicity

No immunogenicity studies were indicated for the one-time use of levonorgestrel for emergency contraception.

## 7.1.11 Human Carcinogenicity

The final pharmacology/toxicology review by Lynnda Reid, PhD states that "there is no evidence of increased risk of cancer with short-term use of steroids," such as the progestin levonorgestrel. This reviewer agrees.

## 7.1.12 Special Safety Studies

None were indicated or performed.

## 7.1.13 Withdrawal Phenomena and/or Abuse Potential

The only withdrawal phenomena that are directly related to the use of 1.5 mg levonorgestrel are vaginal bleeding and the onset of the next menstrual period. Discussion of this data is found in Section 7.1.5.3.

#### 7.1.14 Human Reproduction and Pregnancy Data

From Dr. Reid's pharmacology/toxicology review for this NDA: "While a masculinizing effect of progestins is theoretically possible in female fetuses exposed to levonorgestrel, extensive nonclinical and minimal clinical data indicate no adverse effect of levonorgestrel on the developing female fetus."

There is very limited information specifically on emergency contraception (EC) use during pregnancy since it is taken for the prevention of pregnancy, requires only one or two doses, and will not interrupt an existing pregnancy. A review of the literature on inadvertent use of oral contraceptives (OCs) during pregnancy provides the most information relevant to fetal exposure to sex hormones in early pregnancy. Much of the epidemiological literature dates to the 1970s and 1980s when use of higher-dose oral contraceptives than currently prescribed was the usual practice, and reports of congenital anomalies were being analyzed as to general risk factors and all maternal medications taken around the time of conception or during pregnancy. The doses of sex hormones in EC pills are about 2-5 times that of single OC pills containing the same hormones. However, a course of treatment for EC requires the taking of only one or two doses (total dose of 1.5 mg levonorgestrel) and is not intended for chronic or repeat use. There are many reported cases of women inadvertently taking OCs, either combination hormonal pills containing both an estrogen and a progestin, or progestin-only contraceptive pills, for up to several months while pregnant. This reviewer's comprehensive review of the medical literature on this subject in March 2004 provided strong evidence that exposure to sex hormones (both combination hormonal products and levonorgestrel-alone pills) in early pregnancy does not have a teratogenic effect.

In the WHO 97902 Study, all of the pregnancies were terminated, so there is no data from this large trial on results of full term pregnancy.

From the Nigerian study (N = 1,160): Eleven intrauterine pregnancies were reported; three women in the two dose group and one in the single dose group continued with their pregnancies and delivered live healthy babies.

**Lactation:** Levonorgestrel is secreted into breast milk. Potential exposure of an infant to levonorgestrel can be reduced if the breast-feeding woman takes the tablet immediately after feeding and avoids nursing following levonorgestrel 1.5 mg tablet administration. Orally administered levonorgestrel is found in breast milk at levels approximating a plasma/milk ratio of 100:10-15 (10-15%).

**Reviewer's comment:** At the Advisory Committee meeting to discuss Plan B going over-the-counter (December 16, 2003), the question of breast-feeding as a contraindication was raised. Progestin-only pills, taken continuously for contraception, are in fact labeled as safe for lactating women. It was the Committee's majority opinion that lactation is not a contraindication to taking Plan B (two dose levonorgestrel). The DRUP agrees with this opinion and does not believe that there would be any difference between the two dose and single dose products.

#### 7.1.15 Assessment of Effect on Growth

No assessment of effect on growth was made for the one-time use of 1.5 mg levonorgestrel.

#### 7.1.16 Overdose Experience

The Applicant and the U.S. agent Duramed Pharmaceutical have no reports of intentional overdose with levonorgestrel. There are very limited data on overdosage of 1.5 mg levonorgestrel, although the common adverse events of nausea (and associated vomiting), fatigue, and disruption of the current menstrual cycle might be anticipated. If a large dose of levonorgestrel were ingested, the margin of safety appears to be high and treatment should be symptomatic. The cost of EC would be a deterrent to overuse, and the label clearly states that the product is not for routine contraception. Moreover, in March 2004,

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when an extensive review of levonorgestrel's safety was done by this reviewer, there were no reports of any person overdosing with this product in the Agency's AERS database or in the medical literature.

#### 7.1.17 Postmarketing Experience

There is very limited documented experience with single dose levonorgestrel in the U.S., although it has been used off-label in this manner since the publications of the Nigerian and WHO<sup>6</sup> Study 97902 results in 2002. Single dose 1.5 mg levonorgestrel is approved in some 27 countries worldwide (21 countries use the Gedeon Richter product) and there have been no safety issues with the regimen. Single dose levonorgestrel is available OTC in the Netherlands and Sweden, and directly from a pharmacist without a physician's prescription in eight additional countries. Since the approval in 1999 of the two-dose regimen, in the U.S. alone there have been over \_\_\_\_\_ units of Plan B dispensed and an excellent safety record has been demonstrated. As noted, the Plan B product was approved in August 2006 to go OTC for women age 18 and older; this fact obviously indicates the Agency's assessment of the safety of using a total dose of 1.5 mg levonorgestrel for emergency contraception.

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In September 2006, the FDA's Office of Surveillance and Epidemiology (OSE) reviewed all the adverse event reports naming Plan B or levonorgestrel for emergency contraception found in the FDA's adverse event reporting system (AERS). Of the 166 unduplicated reports (81 U.S.; 85 foreign) there were four reports that noted a single dose regimen, 97 noted a two dose regimen, and 65 were not clearly specified. The following is the Division (DRUP) summary of the OSE review:

- The most frequently reported adverse event was ectopic pregnancy (41) or ruptured ectopic pregnancy (4) with three U.S. and 42 foreign reports. Based on the number of women who have used Plan B or similar emergency contraception, it is not unexpected to have reports of ectopic pregnancy. The absolute failure rate for Plan B is about 1% in clinical trials (i.e., Plan B reduced the expected pregnancy rate from 8% to 1%), and 1-2% of all pregnancies in the general population are reported to be ectopic. Theoretically, based on reported U.S. sales of Plan B of over \_\_\_\_\_ prescriptions, well over \_\_\_\_\_ ectopic pregnancies could have occurred in the U.S. to date associated with a failure of Plan B to prevent pregnancy; yet only three ectopic pregnancies have been reported in U.S. women. Both the failure to prevent pregnancy and the potential for an ectopic pregnancy are addressed in product labeling.
- The majority of the 38 hospitalizations (11 U.S., 27 foreign) were due to ectopic pregnancies (23/38 reports). Compared to the ectopic and hospitalization data reported in the DRUP March 2004 Safety Review for Plan B, these new data do not suggest any change in the very low risk of ectopic pregnancy associated with the use of Plan B from the risk identified at the time of approval.
- Other reported hospitalizations were related to ongoing pregnancy and delivery (3), spontaneous/induced abortion (3), CNS disorder (3), coagulation disorder (2), GI disorder (2), and other (2).
- Of the five cases reporting congenital abnormalities, four were foreign, and the one U.S. case described only an ectopic pregnancy. The foreign reports were for chromosomal abnormalities (2) and multi-system fetal anomalies (2). Given the number of expected pregnancies with the use of levonorgestrel (~1% of all users), four reports is well below the expected 0.85% incidence of congenital anomalies [ACOG Practice Bulletin. Prenatal Diagnosis of Fetal Abnormalities. May

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<sup>6</sup> Von Hertzen H, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicenter randomized trial. *Lancet* 2002;360:1803-10.

2001; No. 27:1-11]. It is highly unlikely, even with significant underreporting, that exposure to Plan B is associated with the development of congenital abnormalities.

- The one U.S. adult death was in a 21 year old college student who died of a cardiac arrhythmia in April 2006, seven days after taking Plan B; her drug panel report was positive for amphetamine, caffeine, and pseudoephedrine levels. We do not believe that Plan B played a role in this death.

When reviewed by age groups, OSE concluded that the data in AERS do not indicate that adverse events in adolescents (age 14-19) are different from those seen in older age groups. However, the data in AERS cannot be used to estimate the actual number of women using levonorgestrel for emergency contraception nor the incidence of adverse events associated with its use.

Based on the information provided by 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.

Gedeon Richter submitted their periodic safety update report (PSUR) covering their global sales from January 1, 2006 to June 30, 2006. There were \_\_\_\_\_ sales of two dose 0.75 mg levonorgestrel and \_\_\_\_\_ sales of single dose 1.5 mg levonorgestrel. Gedeon received 105 reports of adverse events during this recent 6-month time period. Twenty-one (21) were listed as "serious/unexpected" (pages 26-32 of the report); however, of these 21 reports, 20 were for pregnancies and 1 for pruritus. No ectopic pregnancies or life threatening events were reported.

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**Reviewer's comment:** The WHO global guidelines for dispensing hormonal emergency contraceptives, including single dose 1.5 mg levonorgestrel, do not require extensive screening procedures or a physical exam, further reinforcing the widespread agreement about the method's safety. The WHO guideline concludes that as opposed to posing unacceptable safety risks, increased availability of emergency contraception (such as OTC availability) with a simple single dose treatment will likely save lives by reducing maternal mortality associated with an ongoing pregnancy or an abortion.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

The patient exposure and safety assessments were adequate as discussed in the sections below.

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 7.2.1.1 Study type and design/patient enumeration

See Section 7.1 above.

#### 7.2.1.2 Demographics

There were no differences in baseline characteristics between the two levonorgestrel groups at admission. Women were young (mean 27 years), had a mean weight of 56 kg and about one fourth (26%) had used emergency contraception in the past. About 60% of the ITT population had previously been pregnant, and about half of this population (52%) requested emergency contraception because they had not used any contraception at coitus. In all, 44% of women requested treatment within 24 hours, 73% within 48 hours, 89% within 72 hours and 96% within 96 hours. A total of 303 (11%) of the 2,756 subjects who were administered levonorgestrel were > 72 hours from the time of unprotected intercourse. Relating to

ethnicity, 54% of the participants were Chinese, 12% were non-Chinese Asian or Black, and 34% were Caucasian in each treatment group.

**Table 16 Demographic/Ethnic Characteristics**

Women Characteristics	Levonorgestrel 1 dose			Levonorgestrel 2 dose		
	N	Mean	SD*	N	Mean	SD
Age (years)	1356	27.1	7.2	1356	27.4	7.1
Weight (kg)	1355	56.0	8.7	1356	56.4	8.7
Height (cm)	1355	163.1	6.2	1356	163.0	6.0
BMI (kg/m <sup>2</sup> )	1355	21.0	2.8	1356	21.2	2.9
Length of Cycle (days)	1356	29.2	2.7	1356	29.3	2.8
Duration of Menstrual flow (d)	1356	5.0	1.3	1356	5.0	1.2
<b>Ethnic Group</b>		<b>N</b>	<b>%</b>		<b>N</b>	<b>%</b>
<b>Chinese</b>	1356	733	54	1356	732	54
<b>Asian/Black</b>	1356	163	12	1356	166	12
<b>Caucasian</b>	1356	460	34	1356	458	34

\*Standard Deviation

Source: Applicant's Summary of Clinical Safety, Table 4, pg. 9.

### 7.2.1.3 Extent of exposure (dose/duration)

As noted in Section 7.1 above, there were 1,379 women exposed to single dose 1.5 mg levonorgestrel and 1,377 exposed to two dose levonorgestrel. All subjects had a one time only treatment in the trial. The single exposure is acceptable because the indication is for emergency contraception, which is not intended to be used for routine contraception.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The following were the secondary clinical data sources used to evaluate the safety of levonorgestrel and the potential for a switch or approval for OTC status:

1. The publication of the blinded and randomized Nigerian study by A.O. Arowojolu et al. included in the Applicant's Summary of Clinical Safety
2. Postmarketing data and experience: see Section 7.1.17 for a summary
3. Annual reports for Plan B and review of all the AERS reports for Plan B since its approval in 1999
4. DRUP Safety Review, dated March 24, 2004, for the Applicant's request for Plan B to go OTC
5. The more recent peer-reviewed medical literature on emergency contraception
6. The 12<sup>th</sup> annual meeting of the American Society for Emergency Contraception, attended by this reviewer and several experts from countries worldwide, on October 6, 2006 in New York City
7. Review by Karen Lechter, JD, PhD, of Study 9728, Plan B Label Comprehension Study, submitted in 2003 for the switch to OTC status for NDA 21-045
8. Review by Jin Chen, MD, PhD, of Study 9727, Plan B OTC Actual Use Study, submitted in 2003 for the switch to OTC status for NDA 21-045
9. Memos (reviews) by Curt Rosebraugh, MD, Deputy Director of Division of OTC Products, stating his recommendations for the Plan B switch to OTC status for NDA 21-045

Altogether, this comprised a substantial amount of data to evaluate the safety of levonorgestrel in general and the single dose 1.5 mg levonorgestrel specifically for emergency contraception and the switch to OTC status for two dose levonorgestrel (Plan B).

### 7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience with 1.5 mg levonorgestrel for emergency contraception is adequate. Overall, levonorgestrel has been studied in various doses and regimens for over 35 years for both emergency contraception and routine hormonal contraception.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

None were required.

### 7.2.5 Adequacy of Routine Clinical Testing

The trial design and clinical lab testing were adequate for this treatment indication.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

None were required.

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This section is not applicable. Levonorgestrel has been used for over 35 years for routine hormonal contraception and emergency contraception.

### 7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of data for this product and its specific indication is adequate. Although very few laboratory tests were performed, pregnancy testing (urine hCG levels) and ultrasound dating of pregnancies for the date of conception were crucial and were routinely done.

### 7.2.9 Additional Submissions, Including Safety Update

The annual safety report (P-019) for two dose 0.75 mg levonorgestrel Plan B was submitted on 8-30-06 and had no new safety concerns. The PSUR from Gedeon Richter covering their extensive global sales and adverse event reports for both single dose and two dose levonorgestrel from January 1, 2006 to June 30, 2006 was reviewed and is discussed in Section 7.1.17.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Based on the extensive use of levonorgestrel for emergency contraception there were ten categories of anticipated adverse events, as listed in Table 15. Data for the ten most common likely drug-related adverse events were captured on the daily diary and the CRF that was used for all subjects in the WHO Study 97902. There were no significant limitations of the data and no unanticipated adverse events.