

7.4 General Methodology

There was no pooling of data across studies, explorations for predictive factors, or causality determination in this NDA review. None was indicated or needed to determine the safety or efficacy of single dose 1.5 mg levonorgestrel.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There are no clinical issues with this single dose regimen that is to be taken orally as soon as possible within 72 hours after unprotected intercourse. In the original NDA review for the two dose 0.75 mg levonorgestrel (Plan B), the data clearly showed that efficacy decreased with each 24 hour interval after unprotected sex. The data from the WHO trial for the current NDA is not as compelling in terms of decreased effectiveness. There also is evidence that Plan B and single dose levonorgestrel may be effective in some cases if taken in the 73-120 hour interval. In any case, it makes physiological sense that the sooner levonorgestrel is taken, the greater the chance that it will inhibit or delay ovulation (the primary mechanism of action) and therefore prevent a pregnancy. The label will say that single dose levonorgestrel should be taken as soon as possible within 72 hours of unprotected intercourse.

8.2 Drug-Drug Interactions

The following three paragraphs are from the Applicant's Summary of Clinical Safety: Some drugs accelerate the metabolism of combination hormonal contraceptives taken concurrently. Drugs suspected of having the capacity to reduce the efficacy of oral contraceptives include barbiturates phenytoin, phenylbutazone, rifampicin, ampicillin, griseofulvin and other antibiotics.

There were no formal trials of drug-drug interactions. Subjects in studies of emergency contraception are generally healthy. The number of concomitant medicines used in the clinical trials is too low to support any conclusions. Subjects receiving prescription drugs were to be excluded. Nevertheless, a review of the listings for the WHO/HRP Study (92908) reveals that one study participant (Subject 6, Center 2) received levonorgestrel and carbamazepine (Mazetol) concomitantly and did not become pregnant. Other concomitant medications reported in the levonorgestrel arm of the clinical trial included broad spectrum antibiotics (including tetracycline, sulphonamides, doxycycline, penicillins, cephalosporins, anti-malarials), analgesics (including paracetamol, ibuprofen, aspirin), beta-agonists, inhaled steroids for asthma (prednisolone), thyroxin, iron, decongestants, propranolol, insulin, and Chinese herbal remedies.

Theoretically, the effectiveness of levonorgestrel may be reduced in women receiving long-term therapy with hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampicin. It is not clear whether efficacy of the elevated dose of levonorgestrel for emergency contraception would be affected. It is unlikely, however, that short term administration (one or two doses) of levonorgestrel would have any effect on the microsomal enzyme metabolism of the above mentioned drugs.

8.3 Special Populations

None were studied.

8.4 Pediatrics

This product is not intended for use in premenarcheal pediatric populations. The Applicant has requested a waiver of pediatric studies and the reviewer agrees that this waiver should be granted.

In a cross-study comparison reviewed in November 2003 by Myong-Jin Kim, Pharm D, the systemic exposure to levonorgestrel (LNG) was lower in 22 adolescent females (age 12-16) than in adult females following a single 0.75 mg LNG tablet. However, given that LNG pharmacokinetics are highly variable, it is not clearly evident that lower systemic exposure in the adolescent females will result in higher pregnancy rates. Since the unbound concentrations of LNG were not measured in the adolescent study, it is unclear whether the more physiologically relevant unbound concentrations of LNG are different between the adolescent and adult female groups.

- In adolescent female subjects, the geometric mean LNG C_{max} was 6,715 pg/mL (coefficient of variation [CV] 45.8%) and the mean $AUC_{0-\infty}$ was 86,140 pg/mL (CV 42.9%).
- There was a statistically significant difference between the adolescent and adult females with respect to C_{max} (a mean ratio of adolescents/adults = 0.53, 90% CI of 0.41, 0.68).
- The difference between the two groups with respect to $AUC_{0-\infty}$ was borderline significant with a mean ratio (adolescents/adults) of 0.77 (90% CI of 0.61, 0.98).

Reviewer's comment: There is no clinical or postmarketing evidence that the efficacy or safety of levonorgestrel used for emergency contraception in an adolescent population is different from that in the older age population of reproductive women. Limited clinical studies in young adolescents do not demonstrate a difference in safety or efficacy.

8.5 Advisory Committee Meeting

None was held or indicated. It should be noted that at the December 2003 AC meeting for the application for two dose 0.75 mg levonorgestrel (Plan B, NDA 21-045) to switch to OTC status, the Committee voted strongly in favor of OTC status for Plan B with no age restrictions. Results from the Label Comprehension Study, the Actual Use Study, and an extensive DRUP Safety Review were presented and discussed at the meeting.

8.6 Literature Review

See previous sections.

8.7 Postmarketing Risk Management Plan

None is planned or warranted.

8.8 Other Relevant Materials

If approved as requested by the Applicant, the single dose levonorgestrel will initially be by prescription only. At the same time the two tablet Plan B will be available OTC for women age 18 and older. The naming of the two products (sponsored by the same company) and the different availability of each may be confusing at first. DRUP has held discussions with the Applicant to help minimize any confusion that might occur should this situation arise.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy: The two levonorgestrel regimens are highly effective for emergency contraception. The WHO 97902 study showed that in the full FTT 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 the two time intervals from 0 to 72 hours and from 73 to 120 hours.

The Arowojolu et al. study in Nigeria⁷ is supportive of the effectiveness of both levonorgestrel regimens taken within 72 hours of unprotected intercourse. The study 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, and within 72 hours of unprotected intercourse.
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.
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.
6. Lastly, treatment is for emergency contraception and not for routine contraception.

Safety: The safety profile for single dose 1.5 mg levonorgestrel is based on adequate data from randomized clinical trials and extensive global postmarketing experience and is essentially the same as for the two dose 0.75 mg levonorgestrel (Plan B). The most common adverse events are well-established, listed in the label, and not serious. The benefit/risk ratio is favorable: preventing an unplanned pregnancy and the inherent risks of pregnancy, whether continued or terminated, far outweighs the risk of adverse events associated with taking a single dose of 1.5 mg levonorgestrel.

Single dose 1.5 mg levonorgestrel is safe for either prescription or OTC availability in women of all reproductive ages.

9.2 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).

⁷ *Contraception* 2002;66: 269-273.

9.3 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 submitted to the FDA and to Gedeon Richter, Ltd, no postmarketing actions are recommended at this time.

9.3.1 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.

9.3.2 Required Phase 4 Commitments

None are required or recommended.

9.3.3 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. The Applicant will need to confer with the Office of Non-prescription Products to determine if additional measures will be required for single dose 1.5 mg levonorgestrel to go OTC. 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 or single dose 1.5 mg levonorgestrel.

9.4 Labeling Review

The label proposed by the Applicant is essentially the same as the Plan B label with the appropriate new factual information placed in the following sections: Pharmacokinetics, Clinical Studies, Effects on Menses, and Adverse Reactions. The requested trade names (Plan B — plan B —, and — for the new product were discussed with DRUP, DMETS and the Applicant. The main issue was placing a modifier after the name Plan B (the new single dose product could be confused with the older two dose product). There was no final agreement on the trade name. b(4)

Because the final decision is to give this Application an approvable action, final agreement on the label was not reached. This will be done at a future time when the Applicant submits their response to the Approvable Letter.

9.5 Comments to Applicant

None, other than as previously noted in Section 9.3.3.

10 APPENDICES

10.1 Review of Individual Study Reports

There was only one study report submitted with the NDA and it is reviewed in its entirety in the previous sections.

10.2 Line-by-Line Labeling Review

This section is not applicable. The final labeling review will be done in the future,

10.3 List of Abbreviations

ACOG	American College of Obstetrics and Gynecology
AE	Adverse event
C _{max}	maximum concentration
CMC	Chemistry, Manufacturing and Controls
AERS	Adverse Event Reporting System
AUC	area under the curve
BA/BE	bioavailability/bioequivalence
CI	confidence interval
CRF	case report form
Division	Division of Reproductive/Urology Products
DMETS	Division of Medical Errors and Technical Support
DRUP	Division of Reproductive/Urology Products
EC	emergency contraception
EDC	estimated (calculated) date of conception
FDA	Food and Drug Administration
GCP	good clinical practice
hCG	human chorionic gonadotropin
ITT	intent to treat
IU/L	International Units/liter
LNG	levonorgestrel
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
NDA	New Drug Application
OC	oral contraceptive
ODE	Office of Drug Evaluation
OSE	Office of Surveillance and Epidemiology
OTC	over-the-counter
PF	prevented fraction (percent)
PP	per protocol
PR	pregnancy rate
PSUR	periodic safety update report
RR	relative risk
SD	Standard Deviation
WHO	World Health Organization

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

/s/

Daniel Davis
11/22/2006 03:02:13 PM
MEDICAL OFFICER

Lisa Soule
11/22/2006 03:12:03 PM
MEDICAL OFFICER

I concur with Dr. Davis' conclusion that levonorgestrel 1.5
mg single dose for emergency contraception is safe
and effective for use within 72 hours of
known or suspected contraceptive failure or unprotected intercourse
in women of all reproductive ages.

**DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM**

NDA	21-998
Type of Application	Original
Applicant	Gedeon Richter, Ltd
Proprietary Drug Name	Plan B — b(4)
Established Drug Name	Levonorgestrel
Drug Class	Progestogen
Indications	To prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure
Route of Administration	Oral
Dosage Form	Tablet
Dosage Strength	1.5 mg
CDER Receipt Date	January 24, 2006
PDUFA Goal Date	November 24, 2006
Date of Memorandum	November 22, 2006
Reviewer	Lisa M. Soule, M.D.

1 RECOMMENDATIONS

1.1 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.

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

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of a practitioner licensed by law to administer such drugs." I believe that there are sufficient data supporting the safety and efficacy of levonorgestrel 1.5 mg to approve its use in the OTC setting without an age restriction.

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.

1.2 BASIS FOR RECOMMENDATION REGARDING APPROVABILITY

Data from an adequate and well-controlled randomized trial conducted by the World Health Organization (WHO), supported by a literature publication of a randomized, controlled trial conducted in Nigeria, provide evidence of the efficacy of a single 1.5 mg dose of levonorgestrel in preventing pregnancy following unprotected intercourse. Unplanned and unwanted pregnancies resulting from unprotected intercourse pose significant medical, psychological and social risks. The absence of serious adverse events in the clinical trials and of significant safety signals in postmarketing safety reports for both the two-dose and single dose regimens, attests to the safety of the single dose product. Therefore, the risk/benefit ratio for the single dose LNG 1.5 mg product is favorable and supports approval of the product.

In the current application, the Applicant has requested marketing approval only for prescription availability for women of all ages, and studies typically supplied supporting OTC access (label comprehension and actual use studies) were not initially submitted. However, on November 21, 2006, the Plan B sponsor, Duramed Research (also the U.S. agent for the current Applicant, Gedeon Richter) provided right of reference to Gedeon Richter for the Plan B NDA 21-045 application, including the Plan B label comprehension and actual use studies. These studies were conducted to support the original Plan B application for OTC switch submitted in 2003, and were reviewed by medical officers in the Division of Reproductive and Urologic Products and Division of OTC Drug Products at that time. The label comprehension study included 79 women aged 12-16 years and the actual use study enrolled 29 women aged 14-16 years. In the actual use study, all pregnancies that occurred were in women aged 17 and above.

The Medical Team Leader of the Division of OTC Drug Products, Dr. Andrea Leonard-Segal, concluded in an addendum to her review, dated March 5, 2004 that, based upon a reanalysis the Applicant did upon FDA request of data on teenagers' use of Plan B from the actual use study:

The actual use data is predictive that teenagers 14-17 years of age would use OTC Plan B no less properly than those 18-44 years of age.

Given that the currently proposed dosing regimen is simpler than that for the OTC Plan B product, I find no reason to believe that actual use among women under age 18 would be adversely affected, as compared to the acceptable performance demonstrated in the Plan B actual use study for women aged 14-17. The simplicity of the proposed new regimen using a single, one tablet dose, leads me to conclude that the product can 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. For this reason, I recommend approval of the current application as an OTC product for women of all ages.

1.3 RECOMMENDATION ON RISK MANAGEMENT STEPS AND/OR PHASE 4 STUDIES

1.3.1 Risk Management Steps

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

1.3.2 Phase 4 studies

No phase 4 studies are requested.

2 BACKGROUND

2.1 DESCRIPTION OF PRODUCT

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

The proposed regimen, LNG 1.5 mg single dose, is approved for marketing in over 20 countries (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 labeling for the single dose product submitted by the Applicant.

2.2 REGULATORY HISTORY

Plan B, LNG 0.75 mg tablets (administered in two doses, 12 hours apart), was approved for the indication of emergency contraception in 1999, and a supplement to switch the product from prescription to OTC status was submitted on April 16, 2003. Despite recommendations for approval of this application by this Division, the Office of Drug Evaluation III, the Division of Over-the-Counter Drug Products, the Office of Drug Evaluation V and the Office of New Drugs, as well as by the Non-Prescription Drugs and Reproductive Health Drugs Advisory Committees (voting 23:4 for a switch to OTC status without age restrictions), the Director of the Center for Drug Evaluation and Research (CDER) issued a Not Approvable letter on May 6, 2004 stating that the supplement did not provide sufficient data demonstrating the safety and efficacy of the product for OTC use by women under the age of 16.

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

- Whether a prescription/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

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

Over 47,000 public comments were received and summarized, and on July 31, 2006, the Acting Commissioner notified the Applicant that the Agency had determined that rulemaking was not necessary and that further evaluation of the application was proceeding. Following a meeting with CDER and submission of several amendments, the Applicant proposed revised labeling and a Convenient Access Responsible Education (CARE) program, restricting OTC sales to women aged 18 and above. On August 24, 2006, the Applicant was issued an approval to market Plan B as a prescription product for women under age 18, and as an OTC product for women 18 and above.

During the interval where action on the Plan B application was pending, awaiting the Agency's receipt and review of public comments, a preNDA meeting was held between the Division and the Applicant on January 13, 2006, to discuss the Applicant's plan to submit an NDA for a single-dose version of Plan B, based upon a single randomized clinical trial conducted by the WHO. On January 24, 2006, the Applicant 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 the NDA submission.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Daniel Davis, stated in his review, dated November 22, 2006:

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).

Team Leader Comment

- I concur with Dr. Davis' sentiment, if not with the regulatory route he recommends. I too believe that levonorgestrel 1.5 mg single dose regimen has been shown to be safe and effective for prevention of pregnancy after unprotected intercourse, and that the safety profile is sufficiently benign that the product may appropriately be marketed over the counter. However, I do not believe that levonorgestrel 1.5 mg meets the regulatory requirements stated in 21CFR§330.10(a)(4)(vi) for a product to be available only by prescription; therefore I recommend that an Approvable action be taken, as detailed in Section 1.1.*

3 PREVENTION OF PREGNANCY FOLLOWING UNPROTECTED INTERCOURSE OR A KNOWN OR SUSPECTED CONTRACEPTIVE FAILURE

3.1 OVERVIEW OF CLINICAL PROGRAM

The Applicant submitted data from a large randomized, double-blind, multicenter World Health Organization (WHO) trial (Study 97902). This trial randomized 4,136 women who presented within 120 hours after unprotected intercourse to one of three arms – mifepristone 10 mg, LNG 0.75 mg, administered in two doses 12 hours apart, or LNG 1.5 mg in a single dose. The objectives of the study were (1) to compare the efficacy of a single dose of 10 mg of mifepristone and two levonorgestrel regimens when administered in two doses of 0.75 mg 12 hours apart and in one dose of 1.5 mg for emergency contraception, and (2) to assess whether the same effectiveness can be achieved by extending the postcoital treatment period up to 120 hours.

Team Leader Comment

- *Although the study compared three arms of emergency contraception, as mifepristone is not approved in the US for this indication, the clinical reviews focus on the comparisons of the single dose to the two dose regimen for LNG.*
- *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 of unprotected intercourse; therefore, the clinical review focuses primarily on efficacy when the two regimens are initiated within 72 hours of coitus.*

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

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 the next menses occurred. Subjects in both trials kept records of events including vaginal bleeding or spotting, additional episodes of intercourse, and side effects, including vomiting.

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 02162) and a cross-over bioequivalence study comparing the rate and extent of absorption of levonorgestrel 1.5 mg administered once, vs. Plan B (levonorgestrel 0.75 mg) tablets administered as two tablets 12 hours apart (Study 2990). These are discussed further in Section 5.3.

3.2 DEMOGRAPHICS

Demographic characteristics of the subjects were similar across groups in both studies (see Table 1 and Table 2). Women in the WHO study tended to have lower body mass indices (BMIs) than the Nigerian subjects, and were of multiple ethnicities. They also were less commonly parous and had a lower frequency of prior use of emergency contraception.

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Table 1 Demographics of Subjects in WHO Study (Enrolled within 72 hours of unprotected intercourse)

Women Characteristics	LNG Single Dose N=1198		LNG Two-Dose N=1183	
	Mean	SD	Mean	SD
Age (years)	27.3	7.1	27.3	7.1
Weight (kg)	56.0	8.7	56.3	8.6
Height (cm)	163.1	6.0	163.0	6.0
BMI (kg/m ²)	21.0	2.8	21.2	2.8
Length of Cycle (d)	29.2	2.7	29.4	2.9
Duration of Menstrual flow (d)	5.0	1.3	5.1	1.2
Interval Intercourse-Ovulation (d)	-0.6	5.1	-0.5	5.3
Ethnic Group	n	%	n	%
Chinese	667	55.7	648	54.8
Asian/Black	130	10.9	137	11.6
Caucasian	401	33.5	398	33.6
	%		%	
Parous (%)*	40.6		44.8	
Prior use of emergency contraception (%)*	28.8		25.4	

*Based on all subjects enrolled, while remainder of table includes only women enrolled within 0-72 hours of unprotected intercourse

Source: Adapted from Table 8, p 5, Applicant submission of November 8, 2006

Table 2 Demographics of Subjects in Nigerian Study

Characteristic	LNG Two-Dose (Group A) N=545	LNG Single Dose (Group B) N=573
Mean age (SD)	27.4 (7.0)	26.6 (7.2)
Mean BMI (SD)	26.1 (3.5)	25.8 (3.7)
Mean cycle length (SD)	28.8 (2.6)	28.5 (2.7)
Parous (%)	66.1%	59.3%
Prior use of emergency contraception (%)	39.4%	34.9%

Source: Table 1, reference 1, p 270

3.3 DISPOSITION OF SUBJECTS

Counting only the women who enrolled within 72 hours of unprotected intercourse, the WHO study enrolled 1,218 women to the single dose regimen of LNG, and 1,203 women to the two-dose regimen. Excluding 40 women who were lost to follow-up or considered nonevaluable, (20 or 1.6% of the single dose arm and 20 or 1.7% of the two-dose arm), the efficacy populations were 1,198 women in the single dose regimen and 1,183 women in the two dose regimen (see Table 3).

Table 3 Patient Populations (Enrolled within 72 hours of unprotected intercourse)

Patient Populations	LNG Single Dose N=1198	LNG Two-Dose N=1183
Enrolled Initially	1218	1203
Lost or non-evaluable	19 1	18 2
Full ITT (completed study)	1198	1183
Protocol Violations		
>120 hrs post coitus	N/A	N/A
Abnormal cycle length	3	7
Rhythm method used	21	34
Further acts of coitus	26	25
Restricted ITT	1150	1122
Treatment non-compliance	15	15
Per Protocol Population (PP)	1135	1107

Source: Adapted from Applicant's submission of November 8, 2006, p 9

In the Nigerian study, 1,160 women were randomized, 560 to the two-dose group (Group A) and 600 to the single dose group (Group B). A total of 42 women (3.6%) were lost to follow-up; 15 (2.7%) in Group A and 27 (4.5%) in Group B.

3.4 EFFICACY FINDINGS

3.4.1 Assessment of Efficacy

Data on usual menstrual cycle length, date of last menstrual period and expected date of onset of next menses were collected from subjects upon enrolment. From these data, along with the date and time of unprotected intercourse, the cycle day on which intercourse occurred was determined.

Both the WHO and the Nigerian studies evaluated the observed numbers of pregnancies under each dosing regimen of LNG as compared to the expected number of pregnancies. In both studies, the expected numbers of pregnancies were estimated by multiplying the number of women having unprotected intercourse on each day of the menstrual cycle (relative to the estimated day of ovulation) by the probability of conception on each cycle day. In the WHO study, conception probabilities were obtained by two methods, that of Dixon et al² and the Trussel et al³ modification of the Wilcox⁴ method, which is modified to restrict conception probabilities to non-chemical pregnancies. The two estimates were so close that the data are presented here based solely on the Dixon method. In the Nigerian study, conception probabilities were based on British, North Carolina and pooled data; results are reported based upon the pooled data.

Results were expressed in terms of pregnancy rate in each arm, prevented fraction of pregnancies (calculated as 1- [expected number of pregnancies/observed number of pregnancies]), and as the relative risk of pregnancy in the single dose regimen as compared to the two-dose regimen.

3.4.2 Principal Efficacy Study

The WHO study was double-blinded using a double-dummy method, so that all subjects received four pills initially (either two 5 mg tablets of mifepristone plus two placebo "LNG" tablets [mifepristone arm], two placebo "mifepristone" tablets plus two tablets of LNG 0.75 mg [single dose LNG arm], or two placebo "mifepristone" tablets plus one tablet of LNG 0.75 mg plus one

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placebo “LNG” tablet [two dose LNG arm]). The initial dose was taken under the observation of a study investigator; subjects were then given an additional tablet to take at home, twelve hours later. At that time, subjects self-administered either one placebo tablet (mifepristone and single dose LNG arms) or a second LNG 0.75 mg tablet (two dose LNG arm). Time and date of the second dose administration was recorded by the subject.

A follow-up visit was scheduled approximately seven days after the expected onset of the next menses. Women who had not had bleeding at that point were given pregnancy tests. Women were followed until the end of menses. Women with a negative pregnancy test were scheduled for a second follow-up visit, seven days after the first. Women with a positive pregnancy test underwent ultrasound evaluation to determine the gestational age of the pregnancy. Women who did not return for follow-up were contacted by telephone or home visit, where possible.

3.4.2.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy variables were the pregnancy rate with its 95% confidence interval and the prevented fraction with its 95% confidence interval. These were identified as primary parameters after the study was completed but before unblinding occurred. Efficacy was evaluated in the full intent to treat (ITT, defined as all randomized subjects with any assessment of efficacy available), the restricted ITT (defined as full ITT subjects, excluding all protocol violators) and the per protocol (PP, defined as restricted ITT subjects, excluding women with treatment noncompliance and women who used prohibited concomitant medications) populations. The number of subjects in each subpopulation is shown in Table 3.

The primary efficacy analysis (see Table 4) showed similar prevented fractions for the single dose and two-dose LNG regimens (84% and 79%, respectively). The overlapping confidence intervals for the two regimens indicate that the differences in prevented fraction were not statistically significant.

Table 4 Efficacy Results in WHO Trial (Full ITT Population, enrolled within 72 hours of unprotected intercourse)

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

* PF: prevented fraction of pregnancies

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

Team Leader Comment

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

3.4.2.2 SECONDARY EFFICACY ANALYSIS

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

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between the two dose regimens. The adjusted RR, which controlled for the number of expected pregnancies in each group, was similar (see Table 5).

Table 5 Relative Risk of Pregnancy in WHO Study (Full ITT Population, enrolled within 72 hours of unprotected intercourse)

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

Source: Adapted from Table 5, Applicant's submission of November 8, 2006, p 4

Time of treatment

Efficacy stratified by the time of presentation for emergency contraception was evaluated (see Table 6 and Table 7). The prevented fraction with each regimen was lower among women treated four to 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 the unprotected coitus. Regardless of the time of treatment, there was no statistical difference in prevented fraction between the single dose and two-dose regimens.

Table 6 Efficacy Analysis by Time of Treatment in WHO Study (Full ITT Population)

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

* PF: prevented fraction of pregnancies

Source: Adapted from Section 11.4.1.3.1.1, from Final Study Report Amendment 1, June 13, 2003, pp 2-3

Table 7 Prevented Fraction by Day of Treatment in WHO Study (Full ITT Population)

	Day 1 (0-24 hrs)		Day 2 (25-48 hrs)		Day 3 (49-72 hrs)		Day 4 (73-96 hrs)		Day 5 (97-120 hrs)	
	N	PF*	N	PF	N	PF	N	PF	N	PF
LNG Single Dose	622	79.98	377	93.88	199	76.59	87	81.12	63	44.17
LNG Two-Dose	572	77.66	361	90.07	250	64.79	101	84.78	63	10.03

* PF: prevented fraction of pregnancies

Source: Adapted from Section 11.4.1.3.2, from Final Study Report Amendment 1, June 13, 2003, pp 4-6

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Team Leader Comment

- ***Although the prevented fraction for women treated on day 4 after unprotected intercourse is numerically higher than for women treated on day 1 or day 3, the confidence intervals around the day 4 estimate are very wide, and overlap with those around the point estimates for days 1 and 3.***

Further acts of intercourse

Efficacy, as measured by pregnancy rate, also varied according to whether or not the woman had a further act of unprotected intercourse subsequent to her treatment, although this occurred in only about 2% of the population in each treatment group. Table 8 shows the results for the full ITT population of women who presented from 0-120 hours of unprotected intercourse according to whether or not additional acts of unprotected intercourse subsequent to treatment occurred.

Table 8 Efficacy by Presence or Absence of Additional Acts of Intercourse (Full ITT Population)

Group	N	Observed Pregnancies				Expected Pregnancies	Prevented Fraction		
		#	Rate	95%LL	95%UL	#	PF**	95%LL	95%UL
Additional Act(s) of Unprotected Intercourse									
LNG Single Dose	31	2	6.4516	0.7911	21.422	3.0	33.14	-141.5**	91.90
LNG Two-Dose	30	2	6.6667	0.8178	22.074	1.6	-27.49**	-360.5**	84.56
No Additional Act(s) of Unprotected Intercourse									
LNG Single Dose	1325	18	1.3585	0.8071	2.1385	107.5	83.26	73.54	90.08
LNG Two-Dose	1326	22	1.6591	1.0426	2.5012	104.3	78.90	68.06	86.78

* PF: prevented fraction of pregnancies

** According to the Applicant, a negative result in the point estimate or the lower limit of the confidence interval around the point estimate of the prevented fraction indicates that the observed pregnancies would have exceeded expected pregnancies; thus no fraction of expected pregnancies was prevented. Source: Adapted from Tables 11-32 and 11-32, Final Study Report, February 18, 2003, p 57

In women who did have subsequent unprotected intercourse, the prevented fraction was much lower than that seen in women who had only the single, treated, act of unprotected intercourse (33.1% compared to 83.3% in the single dose arm and -27.49 [indicating that the number of observed pregnancies was greater than expected pregnancies in this subgroup] as compared to 78.9% in the two-dose arm).

Team Leader Comment

- ***While the very small proportion of women who had subsequent unprotected intercourse results in lack of precision around the point estimate of the prevented fraction, these data highlight the importance of discouraging women from having additional unprotected intercourse before the next occurrence of menses. As LNG emergency contraception likely delays ovulation, a woman who has subsequent unprotected intercourse may be at increased risk of pregnancy, as she may be ovulating later than she would anticipate.***
- ***It is also notable that of the 20 pregnancies observed in the full ITT population for the single dose regimen (considering all women regardless of time of presentation, within 120 hours), two of the women (10%) had unprotected intercourse***

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subsequent to treatment, although overall, only 2.3% of women in the full ITT population had additional acts of unprotected intercourse.

Ethnicity

The label for Plan B notes a trend toward lower efficacy in Chinese women. The Applicant assessed efficacy by Chinese and non-Chinese ethnicity to determine whether the same tendency was apparent in the single dose regimen. Table 9 shows the results by ethnicity; the prevented fraction is lower with both regimens in Chinese women, with the difference most pronounced in the two-dose regimen, where the prevented fraction drops from 86.5% in non-Chinese women to 72.3% in Chinese women.

Table 9 Efficacy by Ethnicity (Full ITT Population, enrolled within 72 hours of unprotected intercourse)

Group	N	Observed Pregnancies				Expected Pregnancies	Prevented Fraction		
		#	Rate	95%LL	95%UL	#	PF*	95%LL	95%UL
Chinese Subjects									
LNG Single Dose	687	10	1.4993	0.7212	2.7398	53.0	81.13	65.30	90.95
LNG Two-Dose	648	14	2.1605	1.1861	3.5984	50.6	72.32	53.55	84.87
Non-Chinese Subjects									
LNG Single Dose	531	6	1.1299	0.4158	2.4431	46.7	87.15	72.04	95.29
LNG Two-Dose	535	6	1.1215	0.4127	2.4249	44.3	86.46	70.52	95.03

* PF: prevented fraction of pregnancies

Source: Adapted from Table 9, Applicant's submission of November 8, 2006, p 8

Team Leader Comment

- ***If the fecundity of Chinese women is higher than the population on which the conception day probabilities were derived, the expected numbers of pregnancies might be underestimated, leading to an underestimate of prevented fraction, and therefore of the efficacy of LNG in Chinese women.***

Age

Contraception trials typically use the population aged 35 and under as the primary efficacy population. The WHO trial enrolled women aged 14 to 52 years, although only about 14% of the LNG-exposed women were over 35. The Applicant also assessed efficacy by age ≤ 35 and >35 (Table 10) and showed a higher prevented fraction in the older group.

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Table 10 Efficacy by Age (Full ITT Population, enrolled within 72 hours of unprotected intercourse)

	N	Observed Pregnancies			Expected Pregnancies		Prevented Fraction		
		n	Rate	95%LL	95%UL	n	PF*	95%LL	95%UL
35 years of Age or Less									
LNG Single Dose	1032	15	1.4535	0.8157	2.3860	84.3	82.20	70.64	90.04
LNG Two-Dose	1007	18	1.7875	1.0627	2.8103	81.2	77.85	64.99	88.87
36 years of Age or More									
LNG Single Dose	166	1	0.6024	0.0153	3.3108	15.4	93.52	63.90	99.84
LNG Two-Dose	176	2	1.1364	0.1379	4.0445	13.6	85.32	46.96	98.22

* PF: prevented fraction of pregnancies

Source: Adapted from Applicant's submission of November 8, 2006, p 10

Team Leader Comment

- In contrast to the possible situation with Chinese women, fecundity is likely to be lower in older women; therefore, the expected numbers of pregnancies might be overestimated, leading to an overestimate of prevented fraction, and therefore of the efficacy of LNG in women over 35.*

3.4.3 Supportive Efficacy Study

Women in the Nigerian study were provided either two 0.75 mg LNG tablets (single dose group) or one LNG tablet and a matching placebo tablet (two-dose group) to take in the clinic at the time of enrollment, along with either two placebo tablets (single dose group) or one LNG tablet and a matching placebo tablet (two-dose group) to take 12 hours later, at home. Women were to be followed until menstruation occurred, with home visits made "in case of default."

Team Leader Comment

- It is unclear whether women were followed in a clinic visit or by other method of contact. It is not described how the pregnancies were dated.*

3.4.3.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy variables were pregnancy rate, crude relative risk of pregnancy, estimated reduction in expected pregnancies and the effectiveness of each regimen calculated by the Trussel method⁴. A total of 11 pregnancies were reported, seven in the two-dose regimen and four in the single dose regimen. Results are shown in Table 11. The publication reported that the prevented fraction was statistically significantly greater in the single dose regimen as compared to the two-dose regimen.

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Table 11 Efficacy in Nigerian Study

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

* PF: prevented fraction of pregnancies

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

The relative risk of pregnancy after using the single dose regimen as compared to the two-dose regimen was 0.71 (95% CI 0.14 – 3.36).

Team Leader Comment

- *Discussion with the FDA Statistical Reviewer verified that it is theoretically possible for the prevented fraction to differ statistically significantly between the two dose regimens, despite the overlap in the confidence intervals around the two point estimates. As the actual data from this study were not submitted, it is not possible to confirm the reported statistical results. The published article does not indicate whether appropriate statistical adjustments for multiple comparisons were made.*
- *The prevented fraction in both arms of the Nigerian study was equivalent to, or slightly better than that demonstrated in the WHO study. The relative risk of pregnancy was also slightly more favorable for the single dose regimen in the Nigerian trial than in the WHO trial, but was not statistically significantly different from 1.0 in either trial.*

3.4.3.2 SECONDARY EFFICACY ANALYSIS

Efficacy according to latency between unprotected intercourse and treatment was also assessed. The relative risk of pregnancy with the single dose regimen as compared to the two-dose regimen varied with the latency of treatment: 0.68 for ≤ 24 hour delay from time of unprotected intercourse, 0.47 for treatment within 24-48 hours, and 0.82 for latency of 49-72 hours.

Team Leader Comment

- *The article describing the Nigerian study claims that an inverse relationship was demonstrated between efficacy of the treatment regimens and the time of treatment following unprotected intercourse; however, no detailed data are provided to support this claim. The relative risks of pregnancy comparing the treatment arms stratified by latency of treatment do not show a linear trend.*

Additional acts of intercourse subsequent to LNG treatment were noted to increase the pregnancy rate, from 0.5% among women who had no further unprotected intercourse to 1.1% in the single dose arm and from 1.1% to 1.7% in the two-dose arm.

3.4.4 Additional Analyses Requested by FDA

The Division requested that the original analysis of the WHO trial, which included all women enrolled from 0-120 hours following unprotected intercourse, be supplemented with analysis of the subset of women who enrolled within 0-72 hours, as this is the treatment window requested in the proposed indication. Some of these subset analyses had already been performed by the Applicant upon request of the U.K. Regulatory Authority. The efficacy results reported in this review are based upon the 0-72 hour subset.

3.4.5 Overall Assessment of Efficacy

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

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

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

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

3.5 SAFETY FINDINGS

The safety population in the WHO study included all women who took at least one dose of study medication (1379 in the single dose arm and 1377 in the two-dose arm). The safety data reviewed here include women randomized to either levonorgestrel arm regardless of the latency from the act of unprotected intercourse; women randomized to mifepristone are not included.

In the Nigerian study, 1062 women (518 in the two-dose arm and 544 in the single dose arm) provided sufficient information to assess adverse events and timing of next menses.

3.5.1 Deaths and Serious Adverse Events

There were no deaths in either trial. Three serious adverse events (SAEs) were reported in the WHO trial:

- a ruptured corpus luteum cyst treated surgically eight days following single dose LNG treatment
- acute appendicitis in a subject who received single dose LNG treatment
- an ectopic pregnancy in a subject treated with two-dose LNG

The Nigerian study publication does not describe any of the reported AEs as serious. None of the reported pregnancies was ectopic.

3.5.2 Other Adverse Events

In the WHO study, subjects were given a diary card on which to record occurrence of the following anticipated side effects of treatment:

- Bleeding/spotting
- Nausea or vomiting
- Diarrhea
- Fatigue/weakness
- Dizziness
- Headache
- Breast tenderness
- Lower abdominal pain
- Other complaints

A total of 695 women who received the single dose regimen and 693 women in 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. The most common AEs (those listed above plus delay of menses longer than seven days) are displayed in order of decreasing frequency in Table 12. The incidence of AEs did not differ statistically significantly between the two LNG treatment regimens.

Table 12 Adverse Events in WHO Study

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

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

Women in the Nigerian study reported nausea and vomiting, dizziness, headache, breast tenderness, lower abdominal pain and menorrhagia. Headache, breast tenderness and heavy menses were statistically significantly more common in the single dose group (see Table 13).

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Table 13 Proportion with Adverse Events in Nigerian Study

Adverse Event	LNG Two-Dose (Group A) N=518	LNG Single Dose (Group B) 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*

* p<0.05

Source: Reference 1, Table 2, p 271

Team Leader Comment

- *Women in the Nigerian study were not prompted for specific AEs to report; however, the AE profile is similar to that in the WHO study. The AEs listed on the WHO diary card are those specified in the Adverse Reactions section of the current Plan B label.*

Neither study reported whether women who dropped out or were lost to follow-up had experienced adverse events.

Use of LNG 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 group, 4.5% of women experienced a delay of seven or more days beyond the expected date of menses. Women were asked to characterize their period following treatment as "less, similar, more or much more" than their normal menses. Twelve percent of each group experienced bleeding that was "more" (11% each) or "much more" (1% each) than normal menses.

In the Nigerian trial, 20% of the single dose group had the onset of menses > 7 days after expected, compared to 15% in the two dose group. The rate of "heavy menses" was also greater in the single dose group, as noted above.

Team Leader Comment

- *The impact of LNG treatment, whether by single dose or two-dose regimen, on the menstrual cycle was fairly minimal in the WHO study, whether measured in terms of delay of menses or increased severity of bleeding.*
- *It is unclear whether the definition of "heavy menses" in the Nigerian trial was similar to the "more" or "much more" category in the WHO study. It appears that the impact of LNG on menstrual cycle latency and severity may have been more pronounced in the Nigerian study.*

3.5.3 Postmarketing Safety Findings

A safety update was submitted by the Applicant, providing the periodic safety update report for the period January 1, 2006 to June 30, 2006 prepared by Gedeon Richter Ltd, which markets both 0.75 and 1.5 mg LNG products for emergency contraception. Gedeon Richter estimates that 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 pruritis. 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 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 primary medical reviewer's summary of the OSE review noted that:

- The most frequently reported AE was ectopic (41) or ruptured ectopic pregnancy (4), with three U.S. and 42 foreign reports. The absolute failure rate for Plan B is about 1% in clinical trials, and 1-2% of all pregnancies in the general population are reported to be ectopic. Theoretically, based on reported U.S. Plan B sales of over _____ prescriptions, well over _____ ectopic pregnancies associated with a failure of Plan B to prevent pregnancy would be expected; 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). 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). Based on a failure rate of 1% for Plan B, with up to 90,000 pregnancies expected, this rate is below the expected incidence of congenital anomalies. 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. 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. The Division and OSE do not believe that Plan B played a role in this death.

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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 or the incidence of adverse events associated with its use.

Team Leader Comment

- ***While it is acknowledged that ectopic pregnancies and adverse events in general may be underreported, and that incidence data cannot be determined from the AERS database, the data reported do not raise concern for a worrisome safety profile of LNG used for emergency contraception.***

3.5.4 Overall Assessment of Safety Findings

The safety profile for a single dose regimen of 0.15 mg LNG is similar to that seen with the approved two-dose regimen, which has been found to be safe enough to qualify for OTC availability, at least for women aged 18 and above. There were no serious adverse events likely to be attributable to the drug in the single dose regimen of the pivotal clinical trial. A single ectopic pregnancy occurred in the two-dose arm of the WHO trial, which may be drug-related; however, the occurrence of a single ectopic among 44 pregnancies (based upon the entire safety population presenting within 120 hours of unprotected intercourse) is within the expected range of 1-2%. The Gedeon Richter postmarketing safety data based upon more than _____ uses of

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LNG emergency contraception and AERS reports, upon a background of US uses of Plan B, do not suggest any significant safety concerns.

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3.6 RISK/BENEFIT ANALYSIS OF LEVONORGESTREL 1.5 MG FOR PREVENTION OF PREGNANCY FOLLOWING UNPROTECTED INTERCOURSE OR A KNOWN OR SUSPECTED CONTRACEPTIVE FAILURE

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

4 LABELING ISSUES

As acceptable labeling will vary depending upon whether this product is marketed for prescription-only access, OTC availability, or both, labeling negotiations were not conducted in this review cycle. The trade name proposed by the Applicant, Plan B was not acceptable to the Division or to the Division of Medication Errors and Technical Support (DMETS). The Applicant proposed as an alternate the name Plan B—This is similar to the name recommended by the Division and DMETS – Plan B, with the prominently displayed in close proximity to the name. Further discussion of the trade name was deferred.

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5 RECOMMENDATIONS OF OTHER DISCIPLINES AND DIVISIONS

5.1 TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

The primary Toxicology Reviewer, Lynnda Reid, Ph.D., made the following recommendations in her review dated September 21, 2006:

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

Recommendations for nonclinical studies: None

Recommendations on labeling: Nonclinical portions of the submitted label are acceptable.

5.2 CMC AND PRODUCT MICROBIOLOGY

The primary Chemistry Reviewer, Monica Cooper, Ph.D., made the following recommendations in her review dated November 14, 2006:

This new drug application (21-998) is recommended for APPROVAL from the perspective of chemistry, manufacturing and controls. All deficiencies identified during the NDA review cycle have been resolved.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities.

Pending labeling issues will be addressed in the resubmission.

No phase 4 commitments were recommended.

5.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The drug product used in the WHO trial was LNG 0.75 mg, manufactured by Gedeon Richter Ltd., and equivalent to the Postinor brand marketed in Europe. The single-dose regimen

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consisted of two 0.75 mg LNG tablets taken at once, while the two-dose regimen consisted of one 0.75 mg LNG tablet followed 12 hours later by a second 0.75 mg tablet. The Applicant conducted two pivotal bioavailability/bioequivalence (BA/BE) studies to bridge the clinical trial product to the to-be-marketed single tablet containing 1.5 mg LNG without gelatin.

Study 2990 evaluated the BA/BE of one 1.5 mg LNG tablet without gelatin (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.

Study 02162 compared the single dose BA of one 1.5 mg LNG tablet without gelatin to that of two 0.75 mg tablets of LNG without gelatin, administered 12 hours apart. The geometric mean ratios of AUC_t and AUC_{inf} demonstrated bioequivalence; C_{max} was 134% for the single dose as compared to the two-dose regimen, indicating that a higher maximum concentration is attained when the total dose is administered at one time, rather than divided over 12 hours.

The primary Clinical Pharmacology and Biopharmaceutics Reviewer, Myong-Jin Kim, Ph.D., stated the following in her review dated October 23, 2006:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP-DCP-III) has reviewed NDA 21-998 submitted on January 24, 2006. The overall Human Pharmacokinetic Section is acceptable.

No phase 4 commitments were recommended.

5.4 STATISTICS

The Statistical Reviewer, Sonia Castillo, Ph.D., stated the following in the "Conclusions" of her review dated September 26, 2006:

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

An Addendum to the Statistical review was filed on November 21, 2006, stating that Dr. Castillo reviewed and verified the Applicant's analyses of the subgroup of women presenting for treatment within 72 hours of unprotected intercourse.

5.5 DIVISION OF SCIENTIFIC INVESTIGATION

No study site inspections were requested of the Division of Scientific Investigation (DSI). The primary efficacy study was conducted five years ago under WHO oversight, and DSI inspection was believed to be unnecessary, as the large blinded and randomized trial was studying only a new regimen for a proven product (Plan B) for emergency contraception.

5.6 OFFICE OF DRUG SAFETY/DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

Jinhee Jahng, Pharm.D. of the Division of Medication Errors and Technical Support (DMETS) made the following recommendations in her review dated August 10, 2006:

DMETS does not recommend the use of the proprietary names 'Plan B' and 'Plan B' and

b(4)

Lisa Soule, M.D.
NDA 21-998, Plan B
November 22, 2006

b(4)

These comments were conveyed to the Applicant (see Section 4). DMETS also made recommendations concerning carton and insert labeling, which will be addressed in the next review cycle.

5.7 OFFICE OF DRUG SAFETY/DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS

Corrinne Kulick of the Division of Drug Marketing, Advertising and Communications (DDMAC) made a number of comments about the package insert labeling in her review dated October 10, 2006. These will be conveyed to the Applicant in the next review cycle.

5.8 OFFICE OF DRUG SAFETY/ DIVISION OF SURVEILLANCE, RESEARCH AND COMMUNICATION SUPPORT

Jeanine Best, M.S.N., R.N., P.N.P. of the Division of Surveillance, Research and Communication Support (DSRCS) had the following comments and recommendations in her review dated May 25, 2006:

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

b(4)

The latter comment will be addressed in the next review cycle.

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

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

³ Trussel J et al. New estimates of the effectiveness of Yuzpe regimen of emergency contraception. Contraception 55: 363-9, 1998

⁴ 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

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

/s/

Lisa Soule
11/22/2006 02:41:53 PM
MEDICAL OFFICER

Scott Monroe
11/22/2006 03:18:28 PM
MEDICAL OFFICER
I concur with Dr. Soule that this Application is
Approvable.

NDA: 21-998 [Single-dose levonorgestrel 1.5 mg for emergency contraception]

45 Day Filing Meeting Checklist

CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		
5) Are the requisite number of adequate and well controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?			Stats to answer.
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?		X	We will ask the applicant to do so.
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	X		May need a comment in filing letter that full CRFs may be requested as needed; look OK for now.
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	X		

ITEM	YES	NO	COMMENT
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?		X	Need to verify whether the to-be-marketed product is approved elsewhere; if so, need to request labeling and PMX safety update
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	Yes, for clinical.		
16) From a clinical perspective, is this NDA fileable? If [no], please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

Daniel Davis, MD 2-23-06

 Reviewing Medical Officer / Date

Lisa Soule, MD 2/23/06

 Supervisory Medical Officer/Date

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

/s/

Daniel Davis
2/23/2006 05:06:34 PM
MEDICAL OFFICER

Lisa Soule
2/24/2006 11:56:01 AM
MEDICAL OFFICER