

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-998

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 21-998	Submission Dates: 01/24/2006, 01/09/2009
Brand Name	Plan B One-Step
Generic Name	Levonorgestrel
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Duramed Research Inc.
Relevant IND, NDA	IND 45,796, NDA 21-045
Submission Type	Class 2 resubmission
Formulation; Strength	Tablet; levonorgestrel 1.5 mg
Indication	Emergency contraception

This addendum is to correct the error in the Clinical Pharmacology review (Dr. Hyunjin Kim, DFS, June 22, 2009) of resubmission of the NDA 21-998 (submission dates: 01/24/2006 & 01/09/2009). See the following table 2 in section 12.3 pharmacokinetics of the label. Strikes are used for deletion and double underline is used for addition.

Table 2. Pharmacokinetic Parameter Values Following Single Dose Administration of Plan B One-Step (levonorgestrel) tablet 1.5 mg to 30 Healthy Female Volunteers under Fasting Conditions

	Mean (± SD)				
	C _{max} (ng/mL)	AUC _{0-t} (ng·hr/mL)*	AUC _{0-∞} (ng·hr/mL)*	T _{max} (hr)**	t _{1/2} (hr)
Levonorgestrel	19.14 (<u>9.766</u>)	294.80 (208.80)	307.54 (218.45)	1.67 (1.00-4.00)	27.49- <u>5</u> (5.59 <u>6</u>)

C_{max} = maximum concentration

AUC_{0-t} = area under the drug concentration curve from time 0 to time of last determinable concentration

AUC_{0-∞} = area under the drug concentration curve from time 0 to infinity

T_{max} = time to maximum concentration

t_{1/2} = elimination half life

* N=29

** median (range)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Hyunjin Kim
7/9/2009 04:13:42 PM
BIOPHARMACEUTICS

Myong-Jin Kim
7/9/2009 10:30:00 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-998	Submission Dates: 01/24/2006, 01/09/2009
Brand Name	Plan B One-Step
Generic Name	Levonorgestrel
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Duramed Research Inc.
Relevant IND, NDA	IND 45,796, NDA 21-045
Submission Type	Class 2 resubmission
Formulation; Strength	Tablet; levonorgestrel 1.5 mg
Indication	Emergency contraception

Table of Contents

1	Executive Summary	2
1.1	Recommendation	2
1.2	Phase IV Commitments	2
2	Labeling.....	3

1. Executive Summary

Plan B (NDA 21-045), levonorgestrel tablets consisting of two 0.75 mg doses taken 12 hours apart, was approved for emergency contraception for prescription-only use in women of reproductive age on July 28, 1999. Subsequently, Plan B was approved (NDA 21-045/S-011) for emergency contraception for prescription-only use in women age 17 and younger and for over-the-counter (OTC) use in women age 18 and older on August 24, 2006.

On January 24, 2006, the sponsor submitted NDA 21-998 (levonorgestrel 1.5 mg tablet, Plan B One-Step) to seek approval of Plan B One-Step for emergency contraception. NDA 21-998 received an approvable (AE) action on November 22, 2006. However, the overall human pharmacokinetic section of the submission was acceptable from a Clinical Pharmacology perspective (see Clinical Pharmacology Review of NDA 21-998, DFS date, October 23, 2006, Dr. Myong-Jin Kim). Although the sponsor sought the approval of Plan B One-Step for a prescription-only product for women of reproductive age, the Division found that Plan B One-Step can be used as an OTC product for women age 18 and older. Therefore, the Division requested the sponsor to submit revised labeling for marketing 1.5 mg levonorgestrel tablet as a prescription-only product in women age 17 and younger, and as an OTC product for women age 18 and older. In addition, the safety updates of Plan B One-Step were requested.

The current resubmission is the sponsor's response to the Division's AE letter on November 22, 2006. There were no additional studies related to Clinical Pharmacology submitted. During the review cycle of the current resubmission, there was a court order for FDA to allow distribution of Plan B product without a prescription for women age 17 years and older on March 23, 2009. On April 22, 2009, the agency announced that FDA would comply with the court order on the use of Plan B. Since the distribution plan of OTC or prescription-only use for Plan B One-Step was to rely on Plan B's program, the following label revision of Plan B One-Step reflects the change to meet the FDA's compliance to the court order of Plan B use.

1.1 Recommendation

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

1.2 Phase IV Commitments

None.

5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Hyunjin Kim
6/22/2009 05:29:37 PM
BIOPHARMACEUTICS

Myong-Jin Kim
6/22/2009 10:26:13 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information about the Submission			
	Information		Information
NDA Number	21-998	Brand Name	Pending
OCP Division	DCP - 3	Generic Name	Levonorgestrel 1.5 mg tablet
Medical Division	DRUP	Drug Class	Progestin
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Emergency Contraception
OCPB Team Leader	Ameeta Parekh	Dosage Form	Tablet
		Dosing Regimen	1.5 mg
Date of Submission	January 24, 2006	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Duramed Research Inc.
PDUFA Due Date	November 24, 2006	Priority Classification	S
Division Due Date			

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	2		
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
	Data rich:			
	Data sparse:			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
	solution as reference:			
	alternate formulation as reference:	X	1	
Bioequivalence studies -				
	traditional design; single / multi dose:	X	1	
	replicate design; single / multi dose:			
Food-drug interaction studies:				
	Dissolution:	X		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
	Literature References	X		
Total Number of Studies				
Filability and QBR comments				
		"X" if yes	Comments	
	Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
	Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.	
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date		Myong-Jin Kim		
Secondary reviewer Signature and Date		Ameeta Parekh		

Filing Memo

Clinical Pharmacology Review

NDA: 21-998
IND:
Compound: Levonorgestrel 1.5 mg Tablet
Sponsor: Duramed Research Inc.
Date: February 14, 2006
Reviewer: Myong-Jin Kim

Background:

Duramed Research, Inc, a subsidiary of Barr Pharmaceuticals, Inc. and regulatory agent for Gedeon Richter, Ltd of Budapest, Hungary has submitted an original NDA for levonorgestrel (LNG) 1.5 mg tablet for emergency contraception under a 505(b)(2) application.

LNG 1.5 mg tablet is the single dose version of the FDA approved (approval date, July 28, 1999) and marketed Plan B[®] (2 x LNG 0.75 mg tablets, NDA 21-045) without gelatin. LNG 1.5 mg tablet is a single-dose progestin-only emergency contraceptive. It is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the tablet should be taken as soon as possible within 72 hours of unprotected intercourse.

The sponsor submitted the safety and efficacy data of LNG 1.5 mg tablet in a single-pivotal clinical study (97902). In addition, two pharmacokinetic (PK) studies (02162, 2990) were submitted in support of this NDA.

In the Pivotal Study 97902, efficacy and safety data on a single dose of 1.5 mg LNG was investigated by using 0.75 mg tablets (Postinor-2) and the two tablets were taken at the same time.

“Study 02162, Pilot Randomized, 2-Way Cross-Over Comparative Bioavailability Study of Levonorgestrel (Gedeon Richter Ltd) 1.5 mg Tablets and Levonorgestrel 0.75 mg (Gedeon Richter Ltd) Tablets Administered as 1 x 1.5 mg Single Dose and 1 x 0.75 mg Given Twice Daily in Healthy Subjects Under Fasting Conditions”

Study 02162 compared the bioavailability (BA) of a single 1.5 mg dose of LNG from a 1.5 mg LNG tablet to the BA of LNG from two 0.75 mg LNG tablets (Lot T24009) administered 12 hours apart. LNG 1.5 mg tablet is dose proportional with 0.75 mg LNG containing gelatin free tablet. Both formulations were gelatin-free.

Product Code	Company Responsible for Placing Product on Market/Description	Identification	Expiry Date
A	Gedeon Richter Ltd., Hungary, levonorgestrel 1.5 mg tablet: white, flat tablet, impressed with "GOO" on one side and plain on the other side.	Lot/Batch No.: T24157	10.2002 Manufacturing Date: 04.2002
B	Gedeon Richter Ltd., Hungary (Postinor-2), levonorgestrel 0.75 mg tablet: white, flat tablet, impressed with "INOR" on one side and plain on the other side.	Lot/Batch No.: T24009	04.2003 Manufacturing Date: 04.2002

"Study 2990, A Two-Way, Crossover, Open-Label, Single-Dose, Fasting Bioequivalence Study of Levonorgestrel 1 x 1.5 mg Tablets Versus Plan B 2 x 0.75 mg Tablets in Normal Healthy Non-Smoking Female Subjects"

The objective of this study was to compare the rate and extent of absorption of LNG from a test formulation of LNG Tablets, 1 x 1.5 mg versus the reference LNG Tablets (Plan B) 2 x 0.75 mg under fasting conditions.

Treatment A:

Levonorgestrel Tablets, 1.5 mg

Manufacturer: Barr Laboratories, Inc.

Batch #: T36298; Expiry Date: 06/2005; Manufacturing Date: 06/2003

- Almost white, flat, rimmed tablets of about 8 mm diameter, with an impressed mark of "GOO" on one side.

Treatment B:

Levonorgestrel Tablets (Plan B[®]) 0.75 mg

Manufacturer: By: Gedeon Richter, Ltd. For: Duramed Pharmaceuticals, Inc.

Batch #: T41023; Expiry Date: 01/2008

- Almost white, flat, rimmed tablets of about 6 mm diameter, with an impressed mark of "INOR" on one side.

The sponsor submitted in vitro dissolution testing of LNG tablets in Plan B (LNG 0.75 mg tablet, NDA 21-045) and LNG 1.5 mg tablet formulations.

Formulations

LNG 1.5 mg tablets are manufactured, tested and packaged at Gedeon Richter Ltd. in Budapest, Hungary. The change in the composition of LNG 1.5 mg tablets from the Plan B tablets is the

The proposed commercial product containing 1.5 mg LNG, manufactured by Gedeon Richter Ltd. is marketed outside the U.S. under the names Escapelle, Levonelle One Step, and Postinor-1.

b(4)

Composition	Levonorgestrel 0.75 mg Tablets (Plan B [®])	Levonorgestrel 1.5 mg Tablets
Levonorgestrel	0.75 mg	1.50 mg
Colloidal		
Potato Starch		
Magnesium Stearate		
Gelatin		
Talc		
Corn Starch		
Lactose monohydrate		
Total:		

b(4)

Recommendation:

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 21-998 is fileable.

Pending issues:

- During the Pre-NDA meeting on January 13, 2006, the Division agreed that submission of evidence concerning food effects based upon review of the literature should be submitted within 60 days of the NDA submission.
- A table comparing the different formulations of Plan B product (with gelatin), Levonorgestrel 0.75 mg tablet (gelatin-free), Postinor-2 (with gelatin), and the proposed Levonorgestrel 1.5 mg Tablet (gelatin-free) should be submitted within 60 days of the NDA submission.

Myong-Jin Kim, Pharm.D.

Date

Ameeta Parekh, Ph.D., Team Leader

Date

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Myong-Jin Kim
10/23/2006 08:42:29 AM
PHARMACOLOGIST

Ameeta Parekh
10/23/2006 10:26:55 AM
BIOPHARMACEUTICS

**Clinical Pharmacology Review
Division of Clinical Pharmacology 3**

NDA: 21-998

Brand Name: Pending

Generic Name: Levonorgestrel (LNG)

Sponsor: Duramed Research, Inc.

Relevant IND: 45,796

Relevant NDA: 21-045

Date(s) of Submission: January 24, 2006
March 02, 2006
March 20, 2006
September 26, 2006

Type of Submission: Original NDA

Formulation: Tablet
Strength: LNG 1.5 mg

Indication: Emergency Contraception

Reviewer: Myong-Jin Kim, Pharm.D.

Team Leader: Ameeta Parekh, Ph.D.

OCP Division: Division of Clinical Pharmacology 3

OND Division: Reproductive & Urologic Products

Table of Contents

1	Executive Summary	2
1.1	Recommendation	3
1.2	Phase IV Commitments	3
1.3	Summary of Clinical Pharmacology Findings.....	3
2	Question Based Reviews.....	4
2.1	General Attributes.....	4
2.2	General Clinical Pharmacology	5
2.3	Intrinsic Factors	7
2.4	Extrinsic Factors	8
2.5	General Biopharmaceutics	8
2.6	Analytical Section.....	8
3	Detailed Labeling Recommendations	10
4	Appendices.....	11

4.1 Individual Study Reviews	11
4.2 Cover Sheet and OCP Filing/Review Form.....	15

1. Executive Summary

Duramed Research Inc. submitted a New Drug Application (NDA) for levonorgestrel (LNG) 1.5 mg tablet under Section 505(b)2. The proposed therapeutic indication of LNG 1.5 mg is emergency contraception. It is to be administered orally as a single dose of LNG 1.5 mg tablet within 72 hours after unprotected intercourse or failure of a contraceptive method. Efficacy is better if LNG 1.5 mg tablet is taken as directed as soon as possible after unprotected intercourse. LNG is believed to act as an emergency contraceptive by preventing ovulation or fertilization. In addition, it may inhibit implantation by altering the endometrium. Each tablet contains 1.5 mg of a single active steroid ingredient, LNG.

LNG 1.5 mg is a new strength drug product, similar to the currently marketed Plan B[®] tablet (NDA 21-045, approval date, July 28, 1999, Duramed Research Inc.). Plan B is indicated for emergency contraception and each tablet contains LNG 0.75 mg. One Plan B tablet should be administered orally as soon as possible within 72 hours of unprotected sexual intercourse or failure of a contraceptive method. The second tablet must be taken 12 hours after the first dose. For women age 17 and younger, Plan B is a prescription-only emergency contraceptive. For women age 18 and older, it is available as over-the-counter use (NDA 21-045/S-011, approval date, August 24, 2006, Duramed Research Inc.).

In this submission, the sponsor seeks approval of LNG 1.5 mg for emergency contraception as one single dose. The sponsor proposes that one single dose of LNG 1.5 mg tablet simplifies the treatment and increases the patient compliance and acceptability. To support its approval, the sponsor conducted two pivotal bioavailability/bioequivalence (BA/BE) studies (Study 02162, Study 2990) and one pivotal clinical study (WHO/HRP-Study 97902). Study 02162 compared the single-dose bioavailability from one 1.5 mg LNG tablet to the bioavailability from two 0.75 mg LNG tablets (Postinor-2 without gelatin) administered 12 hours apart. The pivotal BE study 2990 compared the bioavailability of one 1.5 mg LNG tablet to the bioavailability of the same single-dose from two 0.75 mg LNG tablets (clinical trial product, Postinor-2 with gelatin, manufactured by Gedeon Richter, Ltd. marketed outside the U.S.). No additional BA/BE or clinical pharmacology studies were conducted. The test product, LNG 1.5 mg tablets (manufactured by Barr Laboratories, Inc., USA) and the reference product, Plan B 0.75 mg tablets (manufactured by Gedeon Richter, Ltd. of Budapest, Hungary for Duramed Pharmaceuticals, Inc., a subsidiary of Barr Pharmaceuticals, Inc.) used in the pivotal Study 2990 were provided by Barr Laboratories, Inc.

WHO/HRP-Study 97902 was a double-blind, randomized, multi-center study in 4,136 healthy women to compare the efficacy and safety of 1.5 mg LNG taken once to the currently approved regimen of two doses of 0.75 mg LNG tablet (Postinor-2 with gelatin) taken 12 hours apart. The efficacy and safety of LNG 1.5 mg were investigated using two tablets of 0.75 mg LNG (Postinor-2 with gelatin) taken at once. The formulation of Postinor-2 tablets contains gelatin whereas the to-be-marketed 1.5 mg LNG tablets do not. The sponsor confirmed that the formulations and the manufacturing process of Postinor-2 with gelatin and Plan B tablets are the same (see March 2, 2006 submission).

1.1 Recommendation

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.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Two pivotal bioavailability/bioequivalence studies were conducted. Study 2990 compared the bioavailability of one LNG 1.5 mg tablet to the bioavailability of the same single-dose from two 0.75 mg tablets in 30 healthy women. Study 02162 compared the single-dose bioavailability from one LNG 1.5 mg tablet to the bioavailability from two LNG 0.75 mg tablets administered 12 hours apart in 15 healthy women.

Single Dose PK of LNG 1.5 mg

Following single dose administration of LNG 1.5 mg tablet in 30 healthy women, the maximum LNG plasma concentration of 19.14 ± 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 (Study 2990).

Table 1. PK parameters (mean \pm SD) of LNG following single dose administration of LNG 1.5 mg tablet in 30 healthy women

	C_{max} (ng/mL)	AUC_t (ng·hr/mL)*	AUC_{inf} (ng·hr/mL)*	T_{max} (hr)**	$T_{1/2}$ (hr)
LNG 1.5 mg tablet	19.14 ± 9.66	294.80 ± 208.80	307.51 ± 218.45	1.67 (1.00-4.00)	27.49 ± 5.59

* n=29; ** median (min - max)

LNG 1.5 mg x 1 Tablet and Plan B 0.75 x 2 Tablets

Study 2990 compared the bioavailability of one LNG 1.5 mg tablet to the bioavailability of the same single dose from two LNG 0.75 mg tablets under fasting conditions. The geometric mean ratios of C_{max} , AUC_t and AUC_{inf} of LNG were within 80.00 – 125.00%. The LNG 1.5 mg tablet was bioequivalent to the 2 x LNG 0.75 mg tablets when administered as a single 1.5 mg dose.

Table 2. Bioequivalence assessment of LNG 1.5 mg x 1 tablet and LNG 0.75 mg x 2 tablets

PK Parameter	Ratio of Means (Test/Reference)	90% CI
AUC_t	101.51 %	93.05 – 110.74 %
AUC_{inf}	102.01 %	93.31 – 111.52 %
C_{max}	101.60 %	91.97 – 112.25 %

Test = LNG tablet, 1 x 1.5 mg; Reference = LNG tablet (Plan B), 2 x 0.75 mg

LNG 1.5 mg x 1 Tablet and Two LNG 0.75 mg Tablets Taken 12 Hours Apart

Study 02162 compared the single-dose bioavailability from one LNG 1.5 mg tablet to the bioavailability from two LNG 0.75 mg tablets administered 12 hours apart. After administration of a single LNG 1.5 mg tablet, the mean C_{max} increased by 34% and the mean AUC_{inf} decreased by 15% compared to the administration of two LNG 0.75 mg tablets administered 12 hours apart.

Table 3. Bioequivalence assessment of LNG 1.5 mg tablet (Test) vs. LNG 0.75 mg tablet x 2 (Reference)

PK Parameter	Ratio of Means (Test/Reference)	90% CI
AUC_t	84.97 %	80.67 – 89.50 %
AUC_{inf}	85.15 %	80.90 – 89.61 %
C_{max}	134.07 %	122.49 – 146.74 %

Test = LNG tablet, 1 x 1.5 mg; Reference = LNG tablet (Plan B), 2 x 0.75 mg 12 hours apart

No formal food effect study was conducted with the 1.5 mg LNG tablet.

2. Question-Based Review

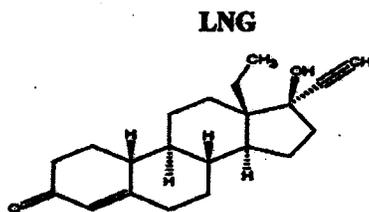
2.1 General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

LNG is a white or practically white odorless powder. It is practically insoluble in water, but soluble in chloroform, and slightly soluble in alcohol. It melts between 232 and 239°C.

Physico-chemical properties

- Structural formula:



- Established Name: Levonorgestrel, USP
- Molecular Weight: 312.4
- Molecular Formula: $C_{21}H_{28}O_2$
- Chemical Name: 18, 19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17a)-, (-)

Drug Formulation

The formulation of the LNG 1.5 mg tablet is based on the LNG 0.75 mg tablet formulation (Plan

B). The only change is the deletion of gelatin in the LNG 1.5 mg tablet (see Formulation under General Biopharmaceutics).

b(4)

Name of the ingredient	Function	Reference to standard	Quantity in one dosage unit
Levonorgestrel	Active ingredient	USP, Richter specification: D-033/4-1	1.50 mg
Colloidal Silicon Dioxide		NF	
Potato Starch		NF	
Magnesium Stearate		NF	
Talc		USP	
Corn Starch		NF	
Lactose monohydrate		NF	
Nominal mass of the tablet:			

b(4)

What are the proposed indication, dosage and route of administration?

LNG 1.5 mg tablet should be taken orally within 72 hours after unprotected intercourse. Efficacy is better if LNG 1.5 mg tablet is taken as directed as soon as possible after unprotected intercourse. LNG 1.5 mg tablet can be used at any time during the menstrual cycle.

b(4)

2.2 General Clinical Pharmacology

What is the proposed mechanism of action?

LNG 1.5 mg tablet is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization. In addition, it may inhibit implantation by altering the endometrium. It is not effective once the process of implantation has begun.

What are the single dose PK parameters of LNG 1.5 mg tablet?

Table 4. PK parameters (mean \pm SD) of LNG following single dose administration of LNG 1.5 mg tablet in 30 healthy women under fasting conditions

	C_{max} (ng/mL)	AUC_t (ng·hr/mL)*	AUC_{inf} (ng·hr/mL)*	T_{max} (hr)**	$T_{1/2}$ (hr)
LNG 1.5 mg tablet	19.14 \pm 9.66	294.80 \pm 208.80	307.51 \pm 218.45	1.67 (1.00 – 4.00)	27.49 \pm 5.59

* n=29; ** median (min – max)

Is single dose of one LNG 1.5 mg tablet bioequivalent to two LNG 0.75 mg tablets given together?

The geometric mean ratios of C_{max} , AUC_t , and AUC_{inf} of LNG were within 80.00 – 125.00 %.

Therefore, a single dose of one LNG 1.5 mg tablet is bioequivalent to two LNG 0.75 mg tablets under fasting conditions.

Table 5. Bioequivalence assessment of 1.5 mg LNG x 1 tablet and 0.75 mg LNG x 2 tablets

PK Parameter	Ratio of Means	90% CI	Intra-subject CV
AUC ₀₋₁₂	101.51 %	93.05 – 110.74 %	19.44 %
AUC _{inf}	102.01 %	93.31 – 111.52 %	19.92 %
C _{max}	101.60 %	91.97 – 112.25 %	22.69 %

Table 6. PK parameters of LNG 1.5 mg x 1 tablet and LNG 0.75 mg x 2 tablets

PK Parameters	Arithmetic Mean ± SD	
	LNG tablet, 1 x 1.5 mg (A) (n=30)	LNG tablets (Plan B) 2 x 0.75 mg (B) (n=30)
AUC ₀₋₁₂ (ng·hr/mL)	294.80 ± 208.80*	269.81 ± 117.25
AUC _{inf} (ng·hr/mL)	307.51 ± 218.45*	279.67 ± 119.30
C _{max} (ng/mL)	19.14 ± 9.66	18.14 ± 6.14
T _{max} (hr)**	1.67 (1.00 – 4.00)	1.33 (1.00 – 3.00)
t _{1/2} (hr)	27.49 ± 5.59*	26.40 ± 4.82

* n=29; ** median (min – max)

How do PK parameters differ following single dose administration of one 1.5 mg LNG tablet and two 0.75 mg LNG tablets administered 12 hours apart?

Study 02162 compared the single-dose bioavailability from one LNG 1.5 mg tablet to the bioavailability from two LNG 0.75 mg tablets administered 12 hours apart. After administration of a single LNG 1.5 mg tablet, the mean C_{max} increased by 34% and the mean AUC_{inf} decreased by 15% compared to the administration of two LNG 0.75 mg tablets administered 12 hours apart.

Table 7. Bioequivalence assessment of LNG 1.5 mg tablet (Test) vs. LNG 0.75 mg tablet x 2 (Reference)

PK Parameter	Ratio of Means (Test/Reference)	90% CI
AUC ₀₋₁₂	84.97 %	80.67 – 89.50 %
AUC _{inf}	85.15 %	80.90 – 89.61 %
C _{max}	134.07 %	122.49 – 146.74 %

Test = LNG tablet, 1 x 1.5 mg; Reference = LNG tablet (Plan B), 2 x 0.75 mg 12 hours apart

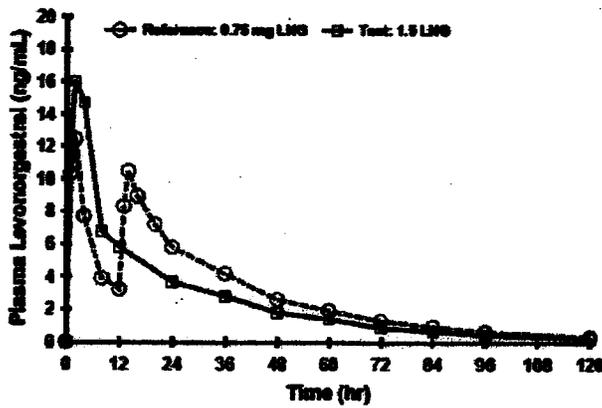
Under fasting conditions, the single dose of one LNG 1.5 mg tablet demonstrated a higher C_{max} and a lower extent of absorption compared to two doses of LNG 0.75 mg tablets taken 12 hours apart.

Table 8. PK parameters (mean \pm SD) of LNG in 15 healthy female subjects

PK Parameter	Test (LNG 1.5 mg)	Reference (LNG 0.75 mg x 2)
AUC _t (ng*hr/mL)	304.98 \pm 83.13	359.85 \pm 99.78
AUC _{inf} (ng*hr/mL)	310.18 \pm 84.03	365.13 \pm 100.28
C _{max} (ng/mL)	18.47 \pm 4.72	13.78 \pm 3.52
T _{max} (hr)*	2.00	2.00
K _{el} (hr ⁻¹)	0.0296 \pm 0.0098	0.0301 \pm 0.0114
T _{1/2} (hr)	26.11 \pm 9.40	26.19 \pm 9.78

*median; Test = LNG 1.5 mg; Reference = LNG 0.75 mg given twice with a 12-hour interval

Figure 1. LNG mean concentration-time profile (N=15)



Test = LNG 1.5 mg; Reference = LNG 0.75 mg given twice with a 12-hour interval

2.3 Intrinsic Factors

Geriatric

LNG 1.5 mg tablet is not intended for use in geriatric (age 65 years or older) populations.

Pediatric

LNG 1.5 mg tablet is not intended for use in pediatric (premenarcheal) populations.

Race

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

Hepatic Insufficiency

No formal studies have evaluated the effect of hepatic insufficiency on the disposition of emergency contraceptive tablets.

Renal Insufficiency

No formal studies have evaluated the effect of renal insufficiency on the disposition of emergency contraceptive tablets.

2.4 Extrinsic Factors

Drug-Drug Interactions

No formal drug-drug interaction studies were conducted.

2.5 General Biopharmaceutics

What are the differences between the clinical and the to-be-marketed formulations?

In the pivotal clinical study, the efficacy and safety of LNG 1.5 mg tablets were investigated using two tablets of 0.75 mg LNG (Postinor-2, manufactured by Gedeon Richter, Ltd.) taken at once. These Postinor-2 tablets contained gelatin. The formulation and manufacturing process of Postinor-2 and Plan B tablets are the same, and they are both manufactured by Gedeon Richter, Ltd., in Hungary. The to-be-marketed formulation of the 1.5 mg LNG tablet is based on the 0.75 mg LNG tablet formulation of Plan B/Postinor-2 products. The only change is the _____ gelatin / _____ in the 1.5 mg LNG tablet, _____

b(4)

Table 9. Formulations of Plan B (LNG 0.75 mg) with (clinical trial formulation) and without gelatin and LNG 1.5 mg tablet without gelatin (to-be-marketed formulation)

	0.75 mg	0.75 mg	1.50 mg
Levonorgestrel Collets			
Potato Starch			
Magnesium Stearate			
Gelatin			
Talc			
Corn Starch			
Lactose monohydrate			
Total:			

b(4)

Study 2990 compared the bioavailability of one LNG 1.5 mg tablet (to-be-marketed formulation) to the bioavailability of the same single-dose from two LNG 0.75 mg tablets (Plan B formulation with gelatin, clinical trial formulation). Study 02162 compared the single-dose bioavailability from one 1.5 mg LNG tablet (to-be-marketed formulation) to the bioavailability from two 0.75 mg LNG tablets (Postinor-2 formulation without gelatin) administered 12 hours apart.

2.6 Analytical

For Study 02162, a High Performance Liquid Chromatographic (HPLC) method with tandem mass spectrometric detection (LC-MS/MS) was performed for the assay of LNG samples _____ For Study 2990, a HPLC method with LC-MS/MS was performed by _____

b(4)

	LNG	
Study No.	02162	2990
Type of Biological Fluid	Plasma	Plasma
Assay Method	LC-MS/MS	LC-MS/MS
Assay		
Sensitivity (LOQ)	0.1 ng/mL	0.05 ng/mL
Recovery	59.37 to 64.07%	52%
Range	0.1 to 20 ng/mL	0.05 to 10 ng/mL
Inter-Assay Precision	5.83 to 8.27%	3.5 to 9.9%
Inter-Assay Accuracy	-8.4 to -0.32%	-2.1 to 0.2%
Intra-Assay Precision	3.22 to 9.52%	2.8 to 11.2%
Intra-Assay Accuracy	-7.56% to 5.00%	-2.5% to 1.3%

- The analytical methods are acceptable. Both accuracy and precision are within acceptable values.

Dissolution Method and Specification

The following dissolution specification has been proposed to the sponsor (see CMC review):

In-Vitro Dissolution Specification:

USP Apparatus 2 (paddles), at 100 rpm, in 500 mL of 0.1 M HCl, 1g/L Sodium Lauryl Sulphate, at 37 ± 0.5 °C

LNG	NLT	@ 30 minutes
-----	-----	--------------

NLT: Not Less Than

Comparative Dissolution

Comparative dissolution testing was conducted using USP Apparatus 2 (paddles), at 75 rpm, in 500 mL of 0.1 M HCl, 1g/L Sodium Lauryl Sulphate, at 37 ± 0.5 °C, with sample collection times at 15, 30, 45, and 60 min. Suitable filtered aliquots of dissolution medium were analyzed by reverse phase HPLC method with UV detection at 254 nm and 200 nm. Please note that the following comparative dissolution data were not reviewed by this reviewer given that a bioequivalence (Study 2990) was conducted to bridge the Plan B formulation with gelatin and LNG 1.5 mg tablet without gelatin.

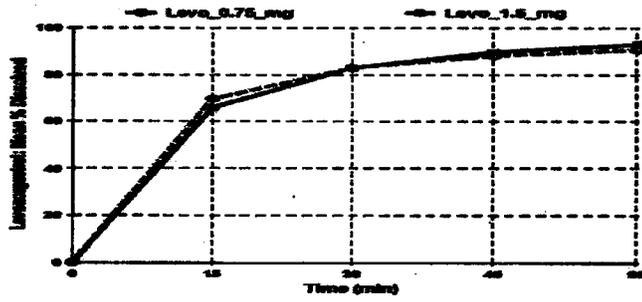
Table 10. Summary of in-vitro dissolution studies

Batch No.	Dosage Form	No. of Dosage Units	Collection Times Mean % Dissolved (range)			
			15 min	30 min	45 min	60 min
LNG 1.5 mg/ T36298	Film-Coated Tablet	12	66.0	83.1	89.8	93.0
LNG 0.75 mg/ T41023	Film-Coated Tablet	12	69.8	83.1	88.2	90.8

b(4)

The dissolution profiles of Plan B (LNG 0.75 mg tablet) and LNG 1.5 mg tablets were compared using f2 equation. For the calculation of f2, three time points (the last at 45 minutes) were used in order to calculate with only one point above 85%. The similarity factor was 79.3.

Figure 2. Dissolution profiles of LNG 1.5 mg and 0.75 mg tablets



3. Detailed Labeling Recommendations

b(4)

b(4)

b(4)

b(4)

4. Appendices

4.1 Individual Study Reviews

Study 02162: Pilot, Randomized, 2-Way Crossover Comparative Bioavailability Study of Levonorgestrel (Gedeon Richter Ltd) 1.5 mg Tablets and Levonorgestrel 0.75 mg (Gedeon Richter Ltd) Tablets Administered as 1 x 1.5 mg Single Dose and 1 x 0.75 mg Given Twice Daily in Healthy Subjects under Fasting Conditions

A single-center, open-label, randomized, two-way crossover relative BA study was conducted in 16 healthy female subjects aged between 18 and 35 years to evaluate the PK parameters of a LNG 1 x 1.5 mg tablet (Gedeon Richter Ltd.) administered as an single dose and a LNG 1 x 0.75 mg tablet (Gedeon Richter Ltd.) given twice with a 12-hour interval. During each study period, a single oral dose of LNG as 1 x 1.5 mg tablet or 1 x 0.75 mg given twice with a 12-hour interval was administered under fasting conditions. The two treatment periods were separated by a washout period of 28 days.

Treatment A: LNG 1.5 mg tablet manufactured by Gedeon Richter Ltd., Hungary, Batch No. T24157

Treatment B: LNG 0.75 mg tablet manufactured by Gedeon Richter Ltd., Hungary, Batch No. T24009

For Treatment A, blood samples were collected pre-dose, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, and 216 hours post-dose. For Treatment B, blood samples were collected at pre-dose, 1, 2, 4, 8, 12, 13, 14, 16, 20, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, and 216 hours post-dose. Blood samples for SHBG were collected prior to drug administration, and at 12, 24, 48, 72, 96, 120, 144, 168, and 192 hours post-dose in each period.

The following PK parameters were determined for LNG: AUC_0 , AUC_{inf} , C_{max} , T_{max} , K_{el} , and $T_{1/2}$. Statistical methods for data analysis consisted of ANOVA for ln-transformed AUC_{inf} , AUC_0 , and C_{max} were determined.

Table 11. PK parameters (mean \pm SD) of LNG in 15 healthy female subjects

PK Parameter	Treatment A (LNG 1.5 mg)	Treatment B (LNG 0.75 mg x 2)
AUC_0 (ng*hr/mL)	304.98 \pm 83.13	359.85 \pm 99.78
AUC_{inf} (ng*hr/mL)	310.18 \pm 84.03	365.13 \pm 100.28
C_{max} (ng/mL)	18.47 \pm 4.72	13.78 \pm 3.52
T_{max} (hr)*	2.00	2.00
K_{el} (hr ⁻¹)	0.0296 \pm 0.0098	0.0301 \pm 0.0114
$T_{1/2}$ (hr)	26.11 \pm 9.40	26.19 \pm 9.78

*median

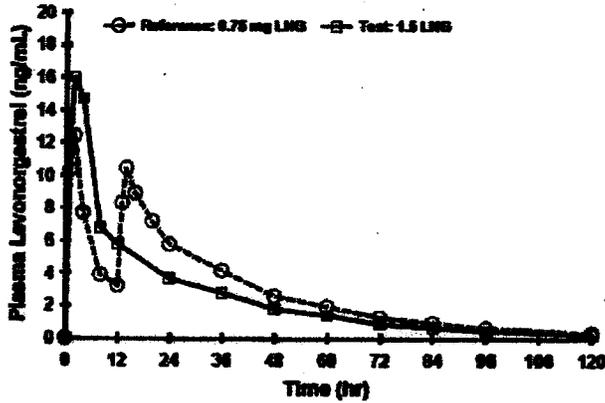
- A single dose of one LNG 1.5 mg tablet (Gedeon Richter Ltd., Hungary, Treatment A) demonstrates a higher rate and a lower extent of absorption compared to one dose of LNG 0.75 mg tablets given twice with a 12-hour interval (Gedeon Richter Ltd., Hungary, Treatment B), under fasting conditions.

Table 12. Bioequivalence Assessment of LNG 1.5 mg tablet (A) vs. LNG 0.75 mg tablet x 2 (B)

PK Parameter	Ratio of Means	90% CI
AUC_0	84.97 %	80.67 – 89.50 %
AUC_{inf}	85.15 %	80.90 – 89.61 %
C_{max}	134.07 %	122.49 – 146.74 %

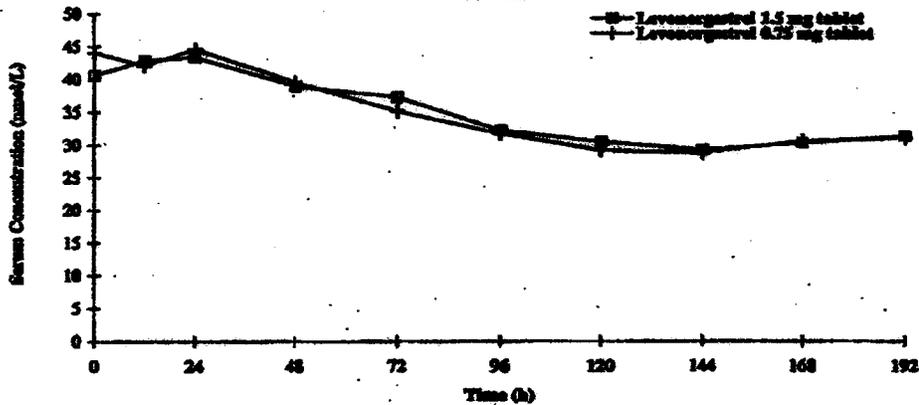
- After administration of a single LNG 1.5 mg tablet, the mean C_{max} increased by 34% and the mean AUC_{inf} decreased by 15% compared to the administration of two LNG 0.75 mg tablets administered 12 hours apart.

Figure 3. LNG mean concentration-time profile (N=15)



Sex Hormone Binding Globulin

Figure 4. SHBG mean concentration-time profile (n=15)



Study 2990: A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Levonorgestrel 1 x 1.5 mg Tablets Versus Plan B 2 x 0.75 mg Tablets in Normal Healthy Non-Smoking Female Subjects

A Phase I, two-way crossover, randomized, open-label, single-dose, bioequivalence study was conducted in 30 healthy, non-smoking female subjects aged between 18 and 45 years. The objective was to compare the rate and extent of absorption of LNG from a test formulation of LNG tablet 1 x 1.5 mg versus the reference LNG tablets (Plan B) 2 x 0.75 mg under fasting conditions. Following an overnight fast of at least 10 hours, one 1.5 mg LNG tablet (Test) or two

0.75 mg LNG tablets (Plan B, Reference) were administered orally with 240 mL of water. The subjects remained fasted for at least 4.5 hours post-dose. There was a 2-week washout period between the two treatments.

Test: LNG Tablet, 1 x 1.5 mg (by Barr Laboratories, Inc, Batch No T36298)
 Reference: LNG Tablet (Plan B), 2 x 0.75 mg (by Gedeon Richter, Ltd. for Duramed Pharmaceuticals, Inc., Batch No T41023)

During each study period, blood samples were drawn at the following time-points: 0 (pre-dose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours post-dose. The following PK parameters for LNG were calculated using standard non-compartmental methods: AUC_t , AUC_{inf} , C_{max} , T_{max} , K_{el} , and $t_{1/2}$. Statistical methods for data analysis consisted of ANOVA for ln-transformed AUC_t , AUC_{inf} and C_{max} . The ratio of geometric means and 90% confidence interval were calculated based on the difference in geometric means of the ln-transformed AUC_t , AUC_{inf} and C_{max} of the test and reference formulations.

Table 13. Bioequivalence Assessment of LNG

PK Parameter	Ratio of Means	90% CI	Intra-subject CV
AUC_t	101.51 %	93.05 – 110.74 %	19.44 %
AUC_{inf}	102.01 %	93.31 – 111.52 %	19.92 %
C_{max}	101.60 %	91.97 – 112.25 %	22.69 %

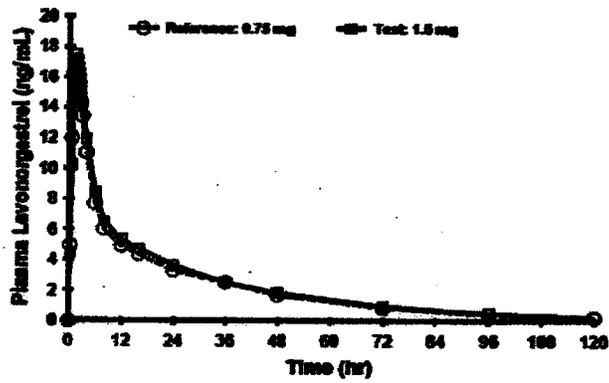
- The geometric mean ratios of C_{max} , AUC_t and AUC_{inf} of LNG were within 80.00 – 125.00 %. Therefore, a single dose of one LNG 1.5 mg tablet is bioequivalent to two LNG 0.75 mg tablets under fasting conditions.

Table 14. PK Parameters of LNG

PK Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	LNG tablet, 1 x 1.5 mg (A) (n=30)	LNG tablets (Plan B) 2 x 0.75 mg (B) (n=30)
AUC_t (ng·hr/mL)	253.21 (70.83)* 294.80 \pm 208.80	247.35 (43.46) 269.81 \pm 117.25
AUC_{inf} (ng·hr/mL)	264.65 (71.04)* 307.51 \pm 218.45	257.26 (42.66) 279.67 \pm 119.30
C_{max} (ng/mL)	17.35 (50.48) 19.14 \pm 9.66	17.08 (33.84) 18.14 \pm 6.14
T_{max} (hr)**	1.67 (1.00 – 4.00)	1.33 (1.00 – 3.00)
$t_{1/2}$ (hr)	27.49 \pm 5.59*	26.40 \pm 4.82

* n=29; ** median (min – max)

Figure 5. LNG mean concentration-time profile



4.2 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology				
New Drug Application Filing and Review Form				
General Information about the Submission				
	Information		Information	
NDA Number	21-998	Brand Name	Feeding	
OCP Division	DCP - 3	Generic Name	Levonorgestrel 1.5 mg tablet	
Medical Division	DRUP	Drug Class	Progestin	
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Emergency Contraception	
OCPB Team Leader	Ameeta Parekh	Dosage Form	Tablet	
		Dosage Regimen	1.5 mg	
Date of Submission	January 24, 2006	Route of Administration	Oral	
Estimated Due Date of OCP Review		Sponsor	Duramed Research Inc.	
FDUFA Due Date	November 24, 2006	Priority Classification	S	
Division Due Date				
Clinical Pharmacology Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

Filing Memo

Clinical Pharmacology Review

NDA: 21-998
IND:
Compound: Levonorgestrel 1.5 mg Tablet
Sponsor: Duramed Research Inc.
Date: February 14, 2006
Reviewer: Myong-Jin Kim

Background:

Duramed Research, Inc, a subsidiary of Barr Pharmaceuticals, Inc. and regulatory agent for Gedeon Richter, Ltd of Budapest, Hungary has submitted an original NDA for levonorgestrel (LNG) 1.5 mg tablet for emergency contraception under a 505(b)(2) application.

LNG 1.5 mg tablet is the single dose version of the FDA approved (approval date, July 28, 1999) and marketed Plan B[®] (2 x LNG 0.75 mg tablets, NDA 21-045) without gelatin. LNG 1.5 mg tablet is a single-dose progestin-only emergency contraceptive. It is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the tablet should be taken as soon as possible within 72 hours of unprotected intercourse.

The sponsor submitted the safety and efficacy data of LNG 1.5 mg tablet in a single-pivotal clinical study (97902). In addition, two pharmacokinetic (PK) studies (02162, 2990) were submitted in support of this NDA.

In the Pivotal Study 97902, efficacy and safety data on a single dose of 1.5 mg LNG was investigated by using 0.75 mg tablets (Postinor-2) and the two tablets were taken at the same time.

“Study 02162, Pilot Randomized, 2-Way Cross-Over Comparative Bioavailability Study of Levonorgestrel (Gedeon Richter Ltd) 1.5 mg Tablets and Levonorgestrel 0.75 mg (Gedeon Richter Ltd) Tablets Administered as 1 x 1.5 mg Single Dose and 1 x 0.75 mg Given Twice Daily in Healthy Subjects Under Fasting Conditions”

Study 02162 compared the bioavailability (BA) of a single 1.5 mg dose of LNG from a 1.5 mg LNG tablet to the BA of LNG from two 0.75 mg LNG tablets (Lot T24009) administered 12 hours apart. LNG 1.5 mg tablet is dose proportional with 0.75 mg LNG containing gelatin free tablet. Both formulations were gelatin-free.

Product Code	Company Responsible for Filing Product on Market/Registration	Identification	Entry Date
A	Gedeon Richter Ltd. Hungary, Levonorgestrel 1.5 mg tablet, white, flat tablet, impressed with "GOC" on one side and plain on the other side.	Lot/Batch No.: T24137	16.3.2002 Manufacturing Date: 04.2002
B	Gedeon Richter Ltd. Hungary (Postinor-2), Levonorgestrel 0.75 mg tablet, white, flat tablet, impressed with "GOC" on one side and plain on the other side.	Lot/Batch No.: T24009	04.2002 Manufacturing Date: 04.2002

"Study 2990, A Two-Way, Crossover, Open-Label, Single-Dose, Fasting Bioequivalence Study of Levonorgestrel 1 x 1.5 mg Tablets Versus Plan B 2 x 0.75 mg Tablets in Normal Healthy Non-Smoking Female Subjects"

The objective of this study was to compare the rate and extent of absorption of LNG from a test formulation of LNG Tablets, 1 x 1.5 mg versus the reference LNG Tablets (Plan B) 2 x 0.75 mg under fasting conditions.

Treatment A:

Levonorgestrel Tablets, 1.5 mg

Manufacturer: Barr Laboratories, Inc.

Batch #: T36298; Expiry Date: 06/2005; Manufacturing Date: 06/2003

- Almost white, flat, rimmed tablets of about 8 mm diameter, with an impressed mark of "GOO" on one side.

Treatment B:

Levonorgestrel Tablets (Plan B[®]) 0.75 mg

Manufacturer: By: Gedeon Richter, Ltd. For: Duramed Pharmaceuticals, Inc.

Batch #: T41023; Expiry Date: 01/2008

- Almost white, flat, rimmed tablets of about 6 mm diameter, with an impressed mark of "TNOR" on one side.

The sponsor submitted in vitro dissolution testing of LNG tablets in Plan B (LNG 0.75 mg tablet, NDA 21-045) and LNG 1.5 mg tablet formulations.

Formulations

LNG 1.5 mg tablets are manufactured, tested and packaged at Gedeon Richter Ltd. in Budapest, Hungary. The change in the composition of LNG 1.5 mg tablets from the Plan B tablets is the

~~_____~~ The proposed commercial product containing 1.5 mg LNG, manufactured by Gedeon Richter Ltd. is marketed outside the U.S. under the names Escapelle, Levonelle One Step, and Postinor-1.

Levonorgestrel	0.75 mg	1.50 mg
Colloidal		
Potato Starch		
Magnesium Stearate		
Gelatin		
Talc		
Corn Starch		
Lactose monohydrate		
Total:		

b(4)

Recommendation:

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 21-998 is fileable.

Pending issues:

- During the Pre-NDA meeting on January 13, 2006, the Division agreed that submission of evidence concerning food effects based upon review of the literature should be submitted within 60 days of the NDA submission.
- A table comparing the different formulations of Plan B product (with gelatin), Levonorgestrel 0.75 mg tablet (gelatin-free), Postinor-2 (with gelatin), and the proposed Levonorgestrel 1.5 mg Tablet (gelatin-free) should be submitted within 60 days of the NDA submission.

Myong-Jin Kim, Pharm.D.

Date

Amceta Parekh, Ph.D., Team Leader

Date

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Myong-Jin Kim
10/23/2006 08:26:45 AM
PHARMACOLOGIST

Ameeta Parekh
10/23/2006 10:29:19 AM
BIOPHARMACEUTICS