CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-998

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-998**
SERIAL NUMBER:	**000 (Resubmission)**
DATE RECEIVED BY CENTER:	**1/12/2009**
PRODUCT:	**Levonorgestrel 1.5 mg Tablets**
INTENDED CLINICAL POPULATION:	**Women desiring emergency (post-coital) contraception**
SPONSOR:	**Gedeon Richter, Ltd.**
DOCUMENTS REVIEWED:	**EDR**
REVIEW DIVISION:	**Division of Reproductive and Urologic Products**
PHARM/TOX REVIEWER:	**Lynnda Reid, Ph.D., Supervisory Pharmacologist**
DIVISION DIRECTOR (Acting):	**Scott Monroe, M.D.**
PROJECT MANAGER:	**Jennifer Mercier**

Date of review submission to Division File System (DFS): 4/22/09

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation 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.

B. Recommendation for nonclinical studies: none

C. Recommendations on labeling: To comply with the Physician's Labeling Rule, the following labeling should replace [redacted] b(4)

Carcinogenicity: There is no evidence of increased risk of cancer with short-term use of progestins. There was no increase in tumorgenicity following administration of levonorgestrel to rats for 2 years at approximately 5 µg/day, to dogs for 7 years at up to 0.125 mg/kg/day, or to rhesus monkeys for 10 years at up to 250 µg/kg/day. In another 7 year dog study administered of levonorgestrel at 0.5 mg/kg/day did increase the number mammary adenomas in treated dogs compared to controls. There were no malignancies.

Genotoxicity: Levonorgestrel was not found to be mutagenic or genotoxic in the Ames Assay, in vitro mammalian culture assays utilizing mouse lymphoma cells and Chinese hamster ovary cells, and in an in vivo micronucleus assay in mice.

Fertility: There are no irreversible effects on fertility following cessation of exposures to levonorgestrel or progestins in general.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Levonorgestrel is a well characterized progestin that is the active component in a number of approved contraceptive drug products. The current maximum dose in conventional oral contraceptives is 0.15 mg/day. The currently approved dosing regimen for emergency contraception is two 0.75 mg LNG tablets taken 12 hours apart.

Levonorgestrel has a toxicologic profile similar to most other progestins in oral contraceptives. Progestins are generally non-toxic, even at fairly high doses, when administered over a short period of time. Doses used in the toxicology studies were > 5000 mg/kg in rodent single dose studies; up to 25 mg/kg/day in rats for 1 year, up to 0.125 mg/kg/day in dogs for 7 years, and 1 mg/kg/day in monkeys for 10 years. There was also a 1 year monkey study with doses up to 2.5 mg/kg/day. The acute 5000 mg/kg doses in rodents are greater than 10,000 times

the proposed dose of 1.5 mg in humans, while the doses used in the chronic animal studies are approximately 2.5, 12 to 30, and 150 times higher in dogs, monkeys and rats, respectively based on body surface area, than the proposed human dose. Teratology studies using doses up to 25 mg/kg in rabbits and 50 mg/kg in rats were negative.

B. Pharmacologic activity: The precise mechanism of action of levonorgestrel in preventing pregnancy is not known. It is thought to work mainly by preventing ovulation and fertilization if intercourse has taken place in the preovulatory phase. Post ovulatory, it may function by causing endometrial changes that discourage implantation. Levonorgestrel 1.5 mg is not effective once the process of implantation has begun.

C. Nonclinical safety issues relevant to clinical use: A single dose of 1.5 mg should pose no significant safety concerns for the user. This high dose of levonorgestrel, which is 10 times higher than the normal oral contraceptive dose, could be fairly androgenic and might have the potential for masculinization of female fetuses exposed in utero. However, there is no evidence of this effect or any teratogenic effects from the animal teratology studies, or from limited human experiences.

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/s/

Lynnda Reid
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PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-998**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**1/24/2006**
PRODUCT:	**Levonorgestrel 1.5 mg Tablets**
INTENDED CLINICAL POPULATION:	**Women desiring emergency (post-coital) contraception**
SPONSOR:	**Gedeon Richter, Ltd.**
DOCUMENTS REVIEWED:	**EDR**
REVIEW DIVISION:	**Division of Reproductive and Urologic Products**
PHARM/TOX REVIEWER:	**Lynnda Reid, Ph.D., Supervisory Pharmacologist**
DIVISION DIRECTOR (Acting):	**Scott Monroe, M.D.**
PROJECT MANAGER:	**Jennifer Mercier**

Date of review submission to Division File System (DFS): October 21, 2006

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation 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.

B. Recommendation for nonclinical studies: none

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

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Levonorgestrel is a well characterized progestin that is the active component in a number of approved contraceptive drug products. The current maximum dose in conventional oral contraceptives is 0.15 mg/day. The currently approved dosing regimen for emergency contraception is two 0.75 mg LNG tablets taken 12 hours apart.

Levonorgestrel has a toxicologic profile similar to most other progestins in oral contraceptives. Progestins are generally non-toxic, even at fairly high doses, when administered over a short period of time. Doses used in the toxicology studies were > 5000 mg/kg in rodent single dose studies; up to 25 mg/kg/day in rats for 1 year, up to 0.125 mg/kg/day in dogs for 7 years, and 1 mg/kg/day in monkeys for 10 years. There was also a 1 year monkey study with doses up to 2.5 mg/kg/day. The acute 5000 mg/kg doses in rodents are greater than 10,000 times the proposed dose of 1.5 mg in humans, while the doses used in the chronic animal studies are approximately 2.5, 12 to 30, and 150 times higher in dogs, monkeys and rats, respectively based on body surface area, than the proposed human dose. Teratology studies using doses up to 25 mg/kg in rabbits and 50 mg/kg in rats were negative.

B. Pharmacologic activity: The precise mechanism of action of levonorgestrel in preventing pregnancy is not known. It is thought to work mainly by preventing ovulation and fertilization if intercourse has taken place in the preovulatory phase. Post ovulatory, it may function by causing endometrial changes that discourage implantation. Levonorgestrel 1.5 mg is not effective once the process of implantation has begun.

C. Nonclinical safety issues relevant to clinical use: A single dose of 1.5 mg should pose no significant safety concerns for the user. This high dose of levonorgestrel, which is 10 times higher than the normal oral contraceptive dose, could be fairly androgenic and might have the potential of masculinization of female fetuses exposed in utero. However, there is no evidence of this effect or any teratogenic effects from the animal teratology studies, or from limited human experiences.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

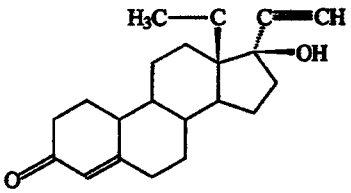
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-998
Review number: 1
Sequence number/date/type of submission: N000 dated 1/24/06
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Gedeon Richter Ltd., Budapest, Hungary
US Agent: Duramed Research, Inc., Bala Cynwyd, PA
Manufacturer for drug substance:

Reviewer name: Lynnda Reid, Ph.D.
Division name: Division of Reproductive and Urologic Products
HFD #: 580
Review completion date: August 17, 2006

Drug:

Trade name:
Generic name: levonorgestrel
Code name: LNG
Chemical name:
a. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17)-(-)-
b. (-)-13-Ethyl-17-hydroxy-18,19-dinor-17 -pregn-4-en-20-yn-3-one
CAS registry number: 797-63-7
Molecular formula/molecular weight: $C_{21}H_{28}O_2$ / 312.45
Structure:



Relevant INDs/NDAs/DMFs: NDA 21-045 (Plan B – LNG 0.75 mg); NDA 21-544 (Seasonale – LNG 0.15 mg/ EE 0.03 mg)

Drug class: synthetic progestin

Intended clinical population: women seeking emergency contraceptive for occasional use after a contraceptive accident or unprotected sex

Clinical formulation: All the components used in the tablet formulation are compendial. The unit formula is summarized in the following table.

Component	Quantity per Tablet (mg)	Function
Levonorgestrel, USP	1.50	API
Colloidal silicon dioxide, NF	[redacted]	
Potato starch, NF		
Magnesium stearate, NF		
Talc, USP		
Corn starch, NF		
Lactose monohydrate, NF		
Total		

b(4)

Route of administration: oral

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-998 are owned by Gedean Richter, Ltd. or are data for which Gedean Richter, Ltd. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-998 that Gedean Richter, Ltd. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Gedean Richter, Ltd. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-998.

Studies reviewed within this submission: No new pharmacology or toxicology studies were submitted. However, relevant toxicology data are available in the published scientific literature. Because of the long history of clinical use of levonorgestrel, there are no perceived new safety concerns related to a single dose of 1.5 mg.

Drug history: Levonorgestrel (LNG) is a second generation synthetic progestin derived from norgestrel. LNG was first approved for use in contraceptive agents in 1996. LNG binds with high affinity to progesterone, androgen, mineralocorticoid and glucocorticoid receptors. While it does not bind to estrogen receptors, it does have strong anti-estrogenic effects.

Levonorgestrel is the active progestin ingredient in numerous oral contraceptives approved for sale in the US and has a toxicologic profile similar to most other progestins used as oral contraceptives. Oral contraceptive products, containing a combination of estrogen ethinyl estradiol and either norgestrel or levonorgestrel were declared safe and effective for emergency contraception by the FDA Advisory Committee in 1997. The current maximum dose of levonorgestrel in OC's is 0.15 mg/day. The currently approved dosing regimen for emergency contraception is two 0.75 mg levonorgestrel tablets taken 12 hours apart. The proposed dosing regime in this NDA is for a single dose of 1.5 mg levonorgestrel.

Pharmacology: The exact mechanism of action for levonorgestrel as an emergency contraception is not known. One of the most plausible biological mechanism of action for the contraceptive effectiveness of levonorgestrel administered post coitally is impairment of follicular maturation and disruption of mechanisms involved in the luteinizing hormone surge, resulting in suppression or delay of ovulation. Post-ovulatory post-ovulatory mechanisms which may be involved include endometrial desynchronization rendering impossible implantation of a fertilized egg, or interference with the fertilization process itself,

e.g., levonorgestrel action on cervical mucus and uterine fluid, interfering with sperm penetration and migration.

Toxicology: Levonorgestrel has a toxicologic profile similar to most other progestins in oral contraceptives. They are generally non-toxic, even at fairly high doses, when administered over a short period of time.

General toxicology: Doses used in the toxicology studies were > 5000 mg/kg in rodent single dose studies; up to 25 mg/kg/day in rats (1 yr study); up to 0.125 mg/kg/day in dogs (7 yr study); and 1 mg/kg/day in monkeys (10 yr study). There was also a 1 year monkey study with doses up to 2.5 mg/kg/day. Teratology studies used doses of levonorgestrel up to 25 mg/kg in rabbits and 50 mg/kg in rats. There were no significant adverse findings in these animal studies.

Genetic toxicology: There is no evidence of genotoxicity in the standard battery of genotoxicity studies.

Carcinogenicity: There is no evidence of increased risk of cancer with short-term use of progestins.

Reproductive toxicology: While a masculinizing effect of progestins is theoretically possible in female fetuses exposed to levonorgestrel, extensive nonclinical and available minimal clinical data indicate no adverse effect of levonorgestrel on the developing female fetus.

Special toxicology: no data submitted

Conclusion: Levonorgestrel is a well characterized progestin that is the active component in a number of approved oral contraceptive drug products. Approval of Levonorgestrel 1.5 mg Tablet is recommended based on 1) the data presented in the original NDA submitted for Plan B (levonorgestrel 0.75 mg), and 2) previous FDA findings of safety in approved contraceptive agents containing levonorgestrel.

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/s/

Lynnda Reid
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PHARMACOLOGIST