

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 21045

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: levonorgestrel; emergency contraception

Reviewer Name: Alex Jordan

Division Name: DRUDP

HFD#: 580

Review Completion Date: 5/21/99

JUN 2 1999

Review number: 1

IND/NDA number: 21-045

Serial number/date/type of submission: 1/29/99; Original NDA

Information to sponsor: Yes () No (X)

Sponsor (or agent): Women's Capital Corp.

Manufacturer for drug substance:

Drug:

Code Name:

Generic Name: levonorgestrel

Trade Name: Plan B

Chemical Name: levonorgestrel

CAS Registry Number: 797-63-7

Molecular Formula/ Molecular Weight: 312.45

Structure:

Relevant INDs/NDAs/DMFs:

Drug Class: contraceptive steroid

Indication: Emergency (post-coital) contraception

Clinical formulation: Two 0.75 mg tablets

Route of administration: oral

Proposed clinical protocol or Use: see indication

OVERALL SUMMARY AND EVALUATION:

Introduction: Levonorgestrel is an approved progestin in oral contraceptives. The current maximum dose in OC's is 0.15 mg/day. The dose recommended for emergency contraception is 1.5 mg. 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); up to 0.125 mg/kg/day in dogs (7 yr studies); and 1 mg/kg/day in monkeys (10 yr study). There was also a 1 yr monkey study with doses up to 2.5 mg/kg/day. Teratology studies used doses up to 25 mg/kg in rabbits and 50 mg/kg in rats.

Safety Evaluation: Levonorgestrel has a toxicologic profile similar to most other progestins in OC's. They are generally non-toxic, even at fairly high doses, when administered over a short period of time. The dose of 1.5 mg should pose no significant safety concerns for the user. This high dose which is 10 times higher than the normal OC dose, could be fairly androgenic and might have the potential of masculinizing the fetus if a woman takes it while pregnant. However, there apparently is no evidence of this from the animal teratology studies, or from the limited number of human experiences.

Clinical Relevance of Safety Issues: Minimal clinical data indicate no adverse effect of Plan B on the developing fetus.

Other Clinically Relevant Issues: None

Conclusions: Animal studies support the safety of the 1.5 mg dose of levonorgestrel.

- Labeling Review (NDA): The pregnancy category has a statement that warnings about fetal effects of OC's has been removed from the OC label. I'm not sure this is relevant to this dose of levonorgestrel, and I recommend its removal.

RECOMMENDATIONS: Pharmacology recommends approval of Plan B for emergency contraception.

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

.. *ISI*
/ 5/28/99

Final labelling is satisfactory

AT 7/12/99

cc: list
NDA 21-045
HFD-580
AJordan

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