

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-874

PHARMACOLOGY REVIEW

REC
10/11/00
8:32AM

NDA 20-874

Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate)

Pharmacia & Upjohn
4S

PM: Jennifer Mercier

Phone: 7-4260

HFD-580

Submission Date: April 7, 2000
User Fee Goal Date: October 7, 2000

Pharmacology Section

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NDA 20-874

Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate)

Pharmacology Review

No review necessary this review cycle.

151

9/27/00

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DEC 23 1997

NDA 20-874

12/23/97

Pharmacia & Upjohn

Submission:

Pharmacology Review of NDA

Drug: Cyclo-Provera (Medroxyprogesterone Acetate and Estradiol Cypionate)

Indication: Contraception

Cyclo-Provera is MPA plus E2 cypionate given together as an injection every 28 days. Both steroids are approved drugs.

The preclinical studies to support this IND were reviewed by Dr. Raheja and his review is appended. Studies have been done on the combination and consist of 18 month study in mice, a 22 month study in rats and a 24 month study in monkeys. No unusual toxicity was noted.

Labeling: Satisfactory

Conclusion: Pharmacology recommends approval of Cyclo-Provera for contraception.

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12/23

Alex Jordan, PhD

NDA 20-874
HFD-580

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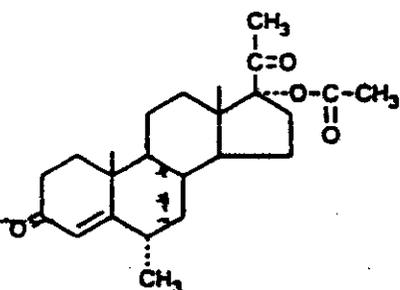
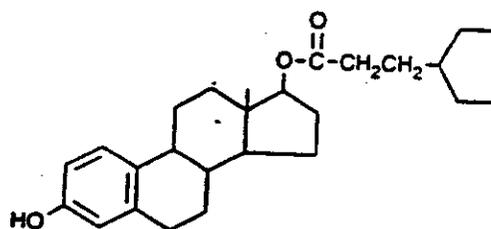
IND 52,624

MAR - 4 1997

Pharmacia & Upjohn Company
Kalamazoo, MichiganSubmission dated: 2-4-1997Received at CDER: 2-5-1997Pharmacology Review of Original IND Submission
Serial NO. 000Drug's trade name: Cyclo-Provera Contraceptive InjectionGeneric name: Medroxyprogesterone acetate and estradiol cypionateCode names:

Medroxyprogesterone acetate - CAS-71-58-9, PNU-8839

Estradiol cypionate - CAS-313-06-4, PNU-3260

CAS names:Medroxyprogesterone acetate: pregn-4-ene-3,20-dione,17-(acetyloxy)-methyl-, (6 α)-Estradiol cypionate: estra-1,3,5 (10)-triene-3,17-diol, (17 β)-,17-cyclopentanepropanoateStructural formulas:Medroxyprogesterone acetateEstradiol cypionateMolecular formulas:

Medroxyprogesterone acetate: C24 H34 O4

Estradiol cypionate: C26 H36 O3

Molecular weights:

386.53

396.57

Indications: Contraception

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Dosage form: Sterile aqueous suspension.

Proposed therapeutic dose: Each 0.5 ml dose vial contains 25 mg Medroxyprogesterone acetate and 5 mg estradiol cypionate is dosed every 28 + 5 days. The dose thus represents 0.5 mg/kg MPA and 0.1 mg/kg of E2C/month.

Composition of Cyclo-Provera Contraception Injection:

<u>Component</u>	<u>Quantity (mg/ml)</u>
Medroxyprogesterone acetate	—
Estradiol cypionate	—
Polysorbate 80 USP	—
Polyethylene glycol USP	—
Sodium chloride USP	—
Methylparaben NF	—
—	—
Sterile water for injection USP	Vehicle

Route of administration: deep intramuscular injection, alternating a deltoid, gluteal or anterior thigh site at each injection.

Related IND and NDAs: IND 1086; NDAs 20-246, 12-541 and 11-839

Rationale for the Cyclo-Provera: It was stated that currently there are 2 injectable progestogen-only contraceptives i.e. Depo medroxyprogesterone acetate and norethisterone enanthate. The review of the progestogen-only contraceptives by WHO in 1982 concluded that there was a need for long-acting reversible contraceptive methods, but expressed a concern regarding the resultant menstrual irregularity as a major reason for discontinuation. In an effort to overcome this problem, combined progestogen and estrogen once-a-month injectable contraceptives were developed.

The progestogen in Cyclo-Provera suppresses ovulation to provide contraception, while estrogen promotes more regular bleeding pattern than progestogen-only injectable contraceptives. The combined injectable contraceptive effects on the endometrium are similar to that of combination oral contraceptives.

Nonclinical pharmacology and toxicology:

Cyclo-Provera Contraceptive Injection is composed of medroxyprogesterone acetate and estradiol cypionate. The safety of medroxyprogesterone acetate as a contraceptive is well established and it is marketed extensively for that indication. The safety of drug combination of medroxyprogesterone acetate and estradiol cypionate was first tested preclinically in 1960s and 1970s by the Upjohn Company and then in humans in multinational clinical trials sponsored by the WHO.

The formulation tested in animals contained 50 mg/ml MPA and 10 mg/ml E2C, which was intended to be marketed as a human contraceptive product. Only summary is presented in the submission and detailed data is not available for review. All studies are non-GLP as these were conducted before the GLP regulations were enforced.

Animal pharmacology: No pharmacology studies have been conducted with Cyclo-Provera. However, expected pharmacological effects were observed as described in the animal toxicity studies.

Animal pharmacokinetics: no PK studies were conducted.

Animal toxicology: Toxicity studies with Cyclo-Provera include acute intraperitoneal mouse and subcutaneous mouse and rat studies, an intramuscular irritation study in rabbits and chronic parenteral toxicity studies in mice, rats and monkeys.

Single-dose toxicity in mice and rats:

LD50 was greater than 2500 mg/kg in mice given the drug intraperitoneally and greater than 1000 mg/kg in mice and rats when given sc. Treatment resulted in decreased activity in mice and body wt loss in mice and rats.

Repeated-dose⁴ toxicity:**18-month mouse study:**

Seven groups of virgin female Upj:TUC(ICR)spf mice (50/g) were used. Groups 1 and 2 were environmental and vehicle controls; groups 3, 4 and 5 received cyclo-provera at dose levels of 2.5, 7.5 and 25 mg/kg respectively (i.e. 5, 15 and 50 x the proposed HTD of 25 mg MPA and 5 mg E2C/month) up to 20 sc injections at approximately monthly intervals. Mice in group 6 received 25

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mg/kg DMPA alone (25x the human dos of 150 mg every 3 months) and those in group 7 mice were injected with 25 mg of E2C/kg alone (250x the human dose of 5 mg every 30 days).

Results:

Clinical signs: no apparent drug-related clinical signs were observed

Mortality: Mice in the 25 mg/kg Cyclo-Provera and E2C groups either died or were sacrificed by 35 and 32 weeks of study respectively. Out of 50 mice in each group 26, 28, 18, 11, 0, 22 and 0 in groups 1 to 7 survived.

Body weight and food consumption: Mice in the 25 mg/kg cyclo-Provera and E2C groups gained sig less but food consumption was greater compared to other groups. Food consumption was also higher in the 7.5 mg/kg Cyclo-Provera group but it was decreased for the DMPA administered group.

Non-neoplastic lesions:

The lesions associated with Cyclo-Provera were increased incidence of pyelitis/pyelonephritis and pyocystitis at high dose only, mammary milk retention cysts, cystic ovaries, increased incidence of hydronephrosis, urinary bladder mucosal hyperplasia and pyometritis. The incidence of cystic endometrial hyperplasia and endometrial hyperplasia were decreased.

With 25 mg/kg E2C alone the incidence of hydronephrosis, pyelitis/pyelonephritis and pyocystitis were increased. Also incidence of gastric ulcers, pyometritis and urinary bladder edema and hemorrhage was higher.

The incidence of cystic endometrial hyperplasia was decreased with DMPA treatment.

Neoplastic lesions: Although no data is submitted, it was reported that no statistically significant increase in the incidence of any type of neoplasm for treated groups as compared with concurrent controls was observed. However, early deaths in the high dose Cyclo-Provera and E2C groups obviated analysis of neoplastic changes in these groups.

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22-month rat study:

The number of dose groups and the dose levels used was similar to that described in the above 18 month mice study. There were 60 virgin female Upj:TUC(SD)spf rats in each group and received up to 22 monthly sc injections. All observations for toxicity, evaluation were similar to those in the mice study except that hemograms and blood chemistry data for 10 rats/g at 390 days and all survivors at 22 months were evaluated and ophthalmologic examination was conducted.

Results:

Clinical signs: there were no apparent drug-related clinical signs.

Survival rate: Out of 60 rats in each group, 34, 41, 18, 10, 0, 35 and 9 rats survived. Survival thus was significantly less for all groups administered Cyclo-Provera or E2C compared with DMPA-treated and controls.

Ophthalmologic changes: ophthalmologic examination revealed no treatment-related changes.

Body weight and food consumption: Rats administered DMPA had increased and those administered E2C had decreased body weight as compared to other groups. Food consumption was comparable.

Hematology and blood chemistry: it was stated that there were no biologically significant treatment-related changes.

Non-neoplastic changes: drug-induced non-neoplastic changes were noted in all groups involving female reproductive tract and in the case of E2C rats only, the mammary glands. These lesions were attributed to chronic hormone administration.

Neoplastic changes: Cyclo-Provera significantly increased the incidence of mammary gland adenocarcinomas in a dose-related manner, values for the 7 groups being 2/47, 1/50, 15/56, 21/59, 29/55, 5/57 and 4/59 respectively. A dose-related increase in the incidence of pituitary adenoma was also observed. The incidence of adrenal gland capsular adenomas was increased in all treated groups. The incidence of pituitary adenomas but not that of mammary gland adenocarcinoma was also increased with E2C treatment. DMPA did not cause an increased incidence of either

tumor type.

2-year monkey study:

Four groups of 6 female Rhesus monkeys were administered i.m. once every 28 days for 2 years Cyclo-Provera at dose levels of 0 (vehicle control), 2.5, 7.5 or 25 mg/kg (5, 15, or 50x the human proposed dose of 25 mg MPA and 5 mg E2C every 30 days).

Results:

Clinical signs: included inhibition of fluid-filled sex skin, an increase in alopecia, and facial redness in the 7.5 mg/kg and 25 mg/kg groups; a marked reduction in vaginal discharge (mensus), emesis a few days after dosing in some treated monkeys and an increase in mammary gland discharge.

Survival rate: 6/6, 6/6, 5/6 and 5/6 monkeys survived in the 4 respective groups.

Body weight: average body weight of treated monkey was higher than controls throughout the study.

Hematology and blood chemistry: no treatment-related changes were reported.

Organ weights: there was increased av. uterine and cervical weights, decreased av. ovarian weight and increased av. pituitary and adrenal weights. These were suggested to be hormonal in nature.

The incidence of pyometra was 0/6, 0/6, 3/6 and 5/6 in group 1, 2, 3 and 4 respectively. Monkeys with signs of pyometra were hysterectomized. Drusen in macula of eye which was observed in 0/6, 1/6, 0/5 and 2/5 monkeys was suggested to be drug-related. There were no toxic drug-related gross or histologic lesions. However, drug-related hormonal changes (organ weight changes, excessive cervical mucus, thin vaginal epithelium, necrotic uterus) were noted in the reproductive tracts of all treated groups, which were dose-related. Ovaries of all treated groups had many corpora albicantia but nocorpora lutea.

Reproductive toxicology: no preclinical reproductive studies were conducted.

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Mutagenic potential: No mutagenicity studies were conducted with Cyclo-Provera.

Carcinogenicity studies: carcinogenicity studies per se were not conducted with Cyclo-Provera although chronic studies in mice and rat were of the same duration as for carcinogenicity studies. These studies were conducted at 50x the proposed human therapeutic dose on body weight basis. No PK data was available to estimate the multiples of human exposure in these studies.

Local tolerance: Six rabbits were administered a single 1 ml dose of the Cyclo-Provera formulation in left lumber muscle and 1 ml of vehicle in right lumber muscle.

Results: the i.m. administered formulation was not irritating to rabbit muscle.

The sponsor has also provided summary of the medroxyprogesterone acetate toxicity studies of duration ranging from a single dose to 28 monthly administrations. Also provided were summaries of studies for reproductive toxicity, mutagenic potential and carcinogenic potential on the basis of which medroxyprogesterone acetate was approved for clinical use as a contraceptive.

Summary of preclinical studies:

LD50 of Cyclo-Provera in mice was greater than 2500 mg/kg when given by ip route and greater than 1000 mg/kg in mice and rats when administered subcutaneously.

The suspension containing 50 mg/ml DMPA and 10 mg/ml E2C was not irritating to rabbit muscle.

Chronic administration of Cyclo-Provera in mice, rats and monkeys for 18, 22 and 24 months respectively at high dose of 50x the human dose on body weight basis, produced no toxic but only hormonal effects in all species. The decreased survival and histologic findings in rodents were considered to be reflection of excessive drug levels. Mammary gland adenocarcinoma and pituitary adenomas were increased in the chronic rat study but not observed in mice or monkeys and thus were considered specific to the administration of high doses of these steroid to rats. From these studies, the sponsor concluded that although safety testing of Cyclo-Provera did not conform to testing of the 90's requirements, studies support the safety of monthly

administration of Cyclo-Provera as contraceptive in humans.

Previous human experience: Cyclo-Provera was initially developed by The Upjohn Company more than 20 years ago and has been used in clinical studies sponsored by the WHO in over 10,000 women in more than 12 countries outside the United States. Both medroxyprogesterone acetate and estradiol cypionate are approved drugs and there is extensive clinical experience with these administered individually.

Proposed clinical program: The sponsor has submitted a protocol entitled "Cyclo-Provera contraceptive injection: A comparative study of safety, patient acceptability and efficacy to Ortho Novum 7/7/7, 28 tablets".

Recommendations: Based on extensive previous clinical experience with medroxyprogesterone acetate and estradiol cypionate along with preclinical experience with medroxyprogesterone acetate and summary results provided for Cyclo-Provera in various animal species and its long term use in humans, Pharmacology considers it safe and has no objection to the initiation of the proposed clinical study.

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Krishan L. Raheja, DVM, PhD

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