CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-583

PHARMACOLOGY REVIEW(S)

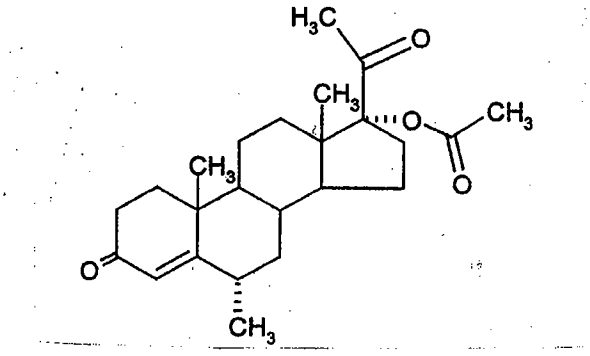
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-583
Review number: 1
Sequence number/date/type of submission: 000/6-30-03/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Pharmacia & Upjohn Company, Kalamazoo, MI
Manufacturer for drug substance: Pharmacia & Upjohn

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.
Division name: DRUDP
HFD #: 580
Review completion date: 9-4-03

Drug: Medroxyprogesterone acetate injectable suspension USP 104 mg/0.65 ml (Depo-Provera SC injection)

Trade name: none given
Generic name (list alphabetically): depot medroxyprogesterone acetate
Code name: -
Chemical name: 17-hydroxy-6a-methylpregn-4-ene-3,20-dione 17-acetate
CAS registry number: -
Mole file number: -
Molecular formula/molecular weight: $C_{24}H_{34}O_4$/344.48
Structure:



Relevant INDs/NDAs/DMFs: IND 61,388

Drug class: progestin

Indication: contraception

Clinical formulation: The formulation for subcutaneous injection is available in pre-filled syringes, each containing 0.65 ml of medroxyprogesterone acetate sterile aqueous suspension, 160 mg/ml. Each 0.65 ml of the SC formulation and 1 ml of the currently approved IM formulation administered one every 3 months contain the following ingredients:

Ingredient	Proposed SC formulation Amount	Currently approved IM formulation Amount
Medoxyprogesterone acetate	104 mg	150 mg
Methylparaben	1.040 mg	1.37 mg
Propylparaben	0.098 mg	0.150 mg
Sodium chloride	5.200 mg	8.68 mg
Polyethylene glycol	18.688 mg	28.9 mg
Polysorbate 80	1.950 mg	2.41 mg
Monobasic sodium phosphate . H_2O	0.451 mg	-
Dibasic sodium phosphate . $12H_2O$	0.382 mg	-
Methionine	0.975 mg	-
Povidone	3.250 mg	-
Water for injection	qs to 0.65 ml	qs to 1 ml

When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

Route of administration: Administered by subcutaneous injection into the anterior thigh or abdomen.

Proposed use: indicated for the prevention of pregnancy in women of child-bearing potential.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: The present formulation is a new formulation of depot medroxyprogesterone acetate (DMPA), which was approved in 1992 as Depo-Provera Contraceptive Injection 150 mg intramuscular (DMPA-IM) for prevention of pregnancy under NDA 20-246. The new formulation differs from the currently approved DMPA-IM in that it has a lower dose (104 mg compared to 150 mg) and will be administered subcutaneously instead of intramuscularly

Since the dosage of the new subcutaneous formulation is lower than the currently approved intramuscular formulation, and systemic exposure is essentially similar with the administration of both formulations, Pharmacology recommends approval of NDA 21-853 for Depo-Provera SC 104 mg to be administered every 3 months.

B. Recommendation for Nonclinical Studies: The subcutaneous formulation of PNU-8839 was evaluated for dose tolerance and potential effects on the injection sites in a pre-clinical toxicity study entitled "PNU-8839: Thirteen-week tolerance study in the female rabbit after subcutaneous injection". Results of this single SC dose of PNU-8839 was associated with no treatment-related mortality and no clinical signs associated with treatment during the 91-days post-dosing observation period. The formulation was slightly less tolerated if it was inadvertently injected into the dermis.

C. Recommendations on Labeling: Labeling is similar to currently approved Depo-Provera Contraceptive Injection 150 mg administered intramuscularly once every 3 months.

II. Summary of Nonclinical Findings: A single study with the proposed Depo-Provera SC injection formulation in female rabbits demonstrated that it was well tolerated locally unless it was inadvertently administered into the dermis.

III. Overview of Nonclinical Findings

A. Pharmacologic Activity: Inhibits the secretion of gonadotropins, which, in turn, prevent follicular maturation and ovulation.

B. Nonclinical Safety Issues Relevant to Clinical Use: The proposed formulation was less well tolerated if inadvertently it was administered into the dermis.

III. Administrative: The present proposed formulation is essentially similar to the currently approved Depo-Provera Contraception Injection 150 mg intramuscularly administered formulation (DMPA-IM) for contraception except that it is to be used subcutaneously at a dosage of 104 mg once every 3 month for the same indication. Based on the clinical experience with the approved DMPA-IM formulation and the proposed formulation along with no significant adverse effects in rabbits via the SC route of administration, Pharmacology recommends approval of NDA 21-583.

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

See review of NDA 20-246 for DMPA-IM formulation

II. SAFETY PHARMACOLOGY:

See review of NDA 20-246 for DMPA-IM formulation

III. PHARMACOKINETICS/TOXICOKINETICS:

No pre-clinical PK is submitted. Pharmacokinetic parameters of MPA after a single SC injection of proposed medroxyprogesterone injectable suspension in healthy women showed a mean C_{max} of 1.56 mg/ml (range — ng/ml), mean Tmax of 8.8 days (range 2.0 – 80.0 days), and mean T1/2 of 43 days (range 16 – 114 days). The corresponding Cmax, Tmax and T1/2 values following a single 150 mg IM dose of currently approved Depo-Provera Contraception Injection were 1 to 7 ng/ml, 3 weeks, and 50 days, respectively (PDR). These data suggest similar PK for the proposed SC formulation and the approved IM formulation of DMPA.

IV. GENERAL TOXICOLOGY:

Study title: PNU-8839: Thirteen-week local tolerance study in the female rabbit after subcutaneous injection

Key study findings: Single SC doses of PNU-8839, vehicle for PNU-8839, and 0.9% saline were well tolerated by female NZW rabbits for up to 91 days postdosing.

Study no: — study No. 695A-301-410-01 & Pharmacia & Upjohn No. (P&T No.) 2001-0395
Volume #, and page #: e-submission, no volume numbers
Conducting laboratory and location: —
Date of study initiation: 10-10-2001
GLP compliance: yes
QA report: yes (*) no ( )
Drug, lot #, radiolabel, and % purity: Batch No. HL0731, not labeled, purity not given
Formulation/vehicle: suspension/as given in composition table. Saline as negative control

Methods (unique aspects):
Dosing:

Species/strain: rabbit/NZW
#/sex/group or time point (main study): 4 females/time point. Each rabbit received a single injection of PNU-8839 in the site to the right of the backbone, 0.9% saline in the site caudal to the formulated drug, and vehicle in the site to the left of the backbone.

Satellite groups used for toxicokinetics or recovery: Four rabbits each were necropsied on Day 7, on Day 28, and on Day 91.
Age: young adult
Weight: 3296 – 3752 grams
Doses in administered units: single dose

Route, form, volume, and infusion rate: subcutaneous, suspension, 0.65 ml containing 104 mg MPA

Observations and times:

Clinical signs: clinical signs once daily and for mortality twice daily
Body weights: On Day –1 and thereafter weekly
Food consumption: daily
Dermal observations: each site was scored for erythema and edema by the method of Draize. Sites were also scored for necrosis, hair loss and scab and scar formation. Sites were scored 24 hours after injection and then daily for the first 7 days and weekly thereafter.
Ophthalmoscopy: -
EKG: -
Hematology: -
Clinical chemistry: -
Urinalysis: -
Gross pathology: at necropsy
Organs weighed: -
Histopathology: Histopathologic evaluation was performed on subcutaneous injection sites on 7, 28, and 91 days after single SC injection of PNU-8839, control vehicle, and 0.9% saline.
Toxicokinetics: -
Other: -

Results:

Mortality: no animals died or sacrificed in moribund condition during the study
Clinical signs: One rabbit for the 91 Day sacrifice was necropsied on Day 28 because of serous ocular discharge, intermittent diarrhea, and reduced food consumption and body weight gain compared to other study rabbits.
Dermal observations: There were no signs of dermal irritation for the vehicle or saline injection sites for any of the 12 rabbits at any time during the study. One rabbit had minimal erythema observed for the site that received PNU-8839 on Day 6 and Day 7 post -dosing and appeared normal during the remaining of the study period. Another rabbit had minimal erythema and/or minimal to slight edema for the site that received PNU-8839 from Day 7 post-dosing through its scheduled termination on Day 28 and this was attributed to inadvertent administration of PNU-8839 into the dermis.
Body weights: generally all gained weight except for one rabbit mentioned above
Food consumption: not affected except for one rabbit mentioned above
Ophthalmoscopy: -
Electrocardiography: -
Hematology: -
Clinical chemistry: -
Urinalysis: -
Organ weights: -
Gross pathology: White to yellowish brown material was evident only in all the 12 rabbits
at the injection site that received PNU-8839.

Histopathology: SC injection of PNU-8839 caused modest localized inflammatory response in all 12 rabbits and showed minimal to slight encapsulation of the test article. In the 2 rabbits that on dermal observations showed slight erythema and edema had slight degeneration of adjacent connective tissue and slight focal myositis in the cutaneous muscle. Less tolerance in these 2 rabbits was attributed to inadvertent partial or complete administration of test article into the dermis.
Toxicokinetics: -

Toxicology summary: No significant treatment related findings were observed

Toxicology conclusions: The proposed formulation was well tolerated unless it was inadvertently injected into the dermis.

Histopathology Inventory for NDA # 321-583
Histopathology was performed only for the skin injection sites

Study	SR 695A-301-410-01			
Species	Rabbit			
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				

Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin	X			
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
*, organ weight obtained

V. GENETIC TOXICOLOGY:

See review of NDA 20-246 for DMPA-IM formulation

VI. CARCINOGENICITY:

See review of NDA 20-246 for DMPA-IM formulation

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

See review of NDA 20-246 for DMPA-IM formulation

VIII. SPECIAL TOXICOLOGY STUDIES:

None submitted

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: The proposed subcutaneous formulation under NDA 21-583 is similar to the currently approved intramuscular formulation (DMPA-IM) under NDA 20-246. Both

formulations are indicated for the prevention of pregnancy. The only difference is the route of administration and the dose is lower for the proposed formulation i.e., 104 mg vs 150 mg once every 3 months. The systemic exposure in humans with the proposed SC formulation was similar to that reported for the currently approved intramuscular formulation. A single SC administration of the proposed formulation was well tolerated in rabbits.

General Toxicology Issues: None

Recommendations: Pharmacology recommends approval of NDA 21-583

Labeling with basis for findings: Labeling is similar to the currently approved DMPA-IM formulation under NDA 20-246.

X. APPENDIX/ATTACHMENTS:

Addendum to review: None

Other relevant materials (Studies not reviewed, appended consults, etc.): None

Any compliance issues: None

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/s/

Krishan L. Raheja
9/9/03 10:10:58 AM
PHARMACOLOGIST

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