CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-843

PHARMACOLOGY REVIEW(S)

Moore

4-1-1997

NDA 20-843

APR - 4 1997

Schering Corporation
Kenilworth, N.J.

Submission dated: 3-10-1997 Received at CDER: 3-11-1997

Pharmacology Review of Original NDA

Drug: Prometrium (Progesterone, USP), Sch 961

Indication: Prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogens tablets.

Dosage form: Soft gelatin capsules 100 mg

Route of administration: Oral

Dosage and administration: Single daily dose of 200 mg orally for 12 days sequentially per 28 day cycle.

Many sections of this NDA make reference to NDA 19-781 (Prometrium capsules for use in secondary amenorrhea) originally submitted on September 30, 1987, and amended on February 8, 1996.

Recommendations: Pharmacology had previously recommended approval of NDA 19-781 for the treatment of secondary amenorrhea (reviews dated 6-13-1996 and 12-2-1996 attached). The present submission is for the same drug product for a new indication i.e., prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women receiving estrogen HRT. Pharmacology now recommends approval of Prometrium capsules for the new indication.

/S/ 4/1/97

Krishan L. Raheja, D.V.M.,Ph.D.

/S/ 4/4

Original NDA 20-843
HFD-345
HFD-580
HFD-580/A.Jordan
HFD-580/K.Raheja, 4-1-1997, N20843.ori

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6-13-1996

NDA 19-781

Schering Corporation
Kenilworth, N.J.

Submission dated: 2-8-1996 Received at CDER: 2-9-1996

Pharmacology Review of NDA Amendment

Drug: Prometrium capsules (progesterone), Sch 961

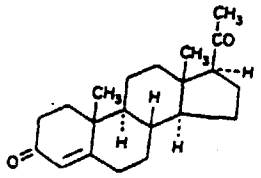
Indication: Secondary amenorrhea

Dosage form: Soft gelatin capsule

Route of administration: Oral

Strength: 100 mg

Structural formula:



Chemical formula: Pregn-4-ene-3,20-dione

Molecular formula: C21 H30 O2

Molecular weight: 314.47

Formulation inactive ingredients: peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow No. 10 and FD&C red No. 40.

Related IND:

This NDA was originally submitted by Besins Pharmaceutical on September 30, 1987 and resubmitted on March 17, 1989 by LaSalle Laboratories (US affiliate of Besins-Iscovesco Pharmaceuticals, Inc) under the trade name Utrogestan capsules. On transfer of the ownership of the NDA to Schering Corporation on July 1, 1990, the trade name of this micronized progesterone product was changed from Utrogestan capsules to Prometrium capsules or SCH 961

capsules.

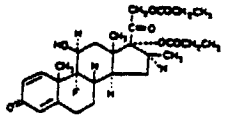
This amendment is in response to Division's non-approvable letter of August 17, 1990.

Preclinical pharmacology and toxicology:

Studies on pharmacology, drug metabolism and toxicology have been reviewed on 5-5-1986 under IND submitted by Besins-Iscovesco Pharmaceuticals, Inc. and on 3-17-1989 under NDA resubmission by La Salle Laboratories. Under the present NDA amendment submission, the sponsor has resummarized the previously submitted studies under IND and NDA and has provided an extensive review of the current literature regarding preclinical drug metabolism, protein binding, genotoxicity, carcinogenicity and reproductive toxicology studies.

In the August 17, 1989 Division's letter to Schering, the sponsor was requested to include a subsection on Carcinogenesis, Mutagenesis and Impairment of fertility in the Precautions section of the proposed drug labeling. The sponsor has complied with Division's request and has included this in the present submission as subsection under the Precautions section of the proposed drug labeling.

Note: The progesterone structural formula given in the proposed drug labeling on page 2, vol 2.2 as shown below is not correct.



Recommendations: Based on the toxicology information provided previously under various IND and NDA submissions as well as extensive literature review now included, Pharmacology has no objection to the approval of the NDA 19-781 for Prometrium capsules for the treatment of secondary amenorrhea.

/S/ 6/13/96

Krishan L. Raheja, DVM, PhD

Original NDA 19781
HFD-345
HFD-510
HFD-510/A.Jordan
HFD-510/K.Raheja, 6-10-1996, N19781.feb.96

/S/ 6/13

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12-2-1996

NDA 19-781

Schering Corporation
Kinilworth. N.J.

Submission dated: 2-8-1996 Received at CDER: 2-9-1996

Addendum to the Pharmacology Review of 6-13-1996 to NDA Amendment

Drug: Prometrium capsules (progesterone), Sch 961

This addendum pertains to changes suggested for the Prometrium labeling. Under the precautions section **Carcinogenesis, Mutagenesis, Impairment of Fertility** the second sentence starting with

should be deleted since it is not supported by any data or literature citations.

Also in the **Overdose** section, references to animal studies without giving actual animal exposure levels and multiples of the human exposure, should be deleted.
It could however, be stated under this title that there is no information on the effect of overdosing in humans.

Recommendations: The sponsor should be requested to make the necessary changes in the Labeling as suggested.

/S/

12/2/96

Krishan L. Raheja, DVM, PhD

Original NDA 19-781
HFD-345
HFD-580
HFD-580/A.Jordan
HFD-580/K.Raheja, 12-2-1996, N19781.Nov96

12/2