CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

CHEMISTRY REVIEW(S)

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

APR 26 1989

NDA 19-781

Division: HFD-510
Chemistry Review # 1

Applicant: La Salle Laboratories
c/o Akin, Gump, Strauss, Hauer & Feld
1333 New Hampshire Ave., NW, Suit 400
Washington, D.C. 20036

Date Completed: 4-20-89

Product Name(s):
Proprietary: Utrogestan
Non-proprietary: Progesterone, USP, Capsules

Dosage Form(s) and Route(s) of Administration:
Soft gelatin capsules, 100 mg for oral use.

Pharmacological Category and/or Principal Indication:
Progestin.

Structural Formula and Chemical Name:

See the USP for this well known steroid.

Initial Submission: 9-30-87

Amendment(s): 3-17-89 consists of a resubmission.

Suporting Documents: IND
DMF
DMF
DMF
DMF
DMF
DMF
An authorization letter from each DMF holder is included in the initial submission to allow refernce to the file on behalf of Besins Iscovesco Pharmaceuticals.

Remarks:
Application was transferred from Besin Pharmaceuticals, Inc. to LaSalle Laboratories on 3-15-89. Besins Pharm. was dissolved on 9-26-88.
Refusal to file letter issued 12-1-87. The 3-17-89 resubmission incorporates by reference the entire original submission of 9-30-87.
The application still provides for as the manufacturer of the drug substance and manufacture of the drug product by

Conclusion and Recommendation:

The application is not approvable under section 505(B)(1) of the Act. Product labels need minor revision.

/S/

Helmut B. Nunn
Review Chemist

cc: IND/NDA Orig.
HFD-510
HFD-102/Kumkumian
HFD-510/HNunn/

R/D initialed by 4/26/89

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS JUN 21 1990

NDA 19-781

Division: HFD-510
Chemistry Review # 2

Applicant: La Salle Laboratories
1717 N Street, N.W.
Washington, D.C. 20036

Date Completed: 12-4-89

Product Name(s):
Proprietary: Utrogestan
Non-proprietary: Progesterone, USP

Dosage Form(s) and Route(s) of Administration:
Soft gelatin capsules, 100 mg for oral use.

Pharmacological Category and/or Principal Indication:
Progestin.

Structural Formula and Chemical Name:

See the USP for this well known steroid.

Initial Submission: 9-30-87

Amendment(s): 7-17-89 submits additional manufacturing controls information.
8-22-89 provides clarifying controls information.
9-5-89 submits a change of address.
9-21 89 consists of notification that samples were submitted to the FDA laboratories.

Supporting Documents: See Chem. Rev. #1.

Remarks:
Chem. Rev. #1 dated 4-20-89 found application not approvable under section 505(B)(1) of the Act. A letter detailing the chemistry deficiencies was sent to the applicant on 5-31-89. The 7-17-89 amendment is in respons to that letter.

Conclusion and Recommendation:

Manufacturing and controls information is now approvable. Methods validation has been successfully completed. However, some modifications of the alternate assay and the assay (Content Uniformity) methods are required.
Labeling is acceptable.

/S/

Helmut B. Nunn
Review Chemist

cc: NDA Orig.
HFD-510
HFD-510/HNunn

R/D initialed by
Wang 1215c

Harrall

JUN 21 1990

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 19-781

Division: HFD-510
Chemistry Review # 3

Applicant: La Salle Laboratories
1717 N Street, N.W.
Washington, D.C. 20036

Date Completed: 6-21-90

Product Name(s):
Proprietary: Utrogestan
Non-proprietary: Progesterone, USP

Dosage Form(s) and Route(s) of Administration:
Soft gelatin capsules, 100 mg for oral use.

Pharmacological Category and/or Principal Indication:
Progestin.

Structural Formula and Chemical Name:

See the USP for this well known steroid.

Initial Submission: 9-30-87

Amendment(s): 1-29-90 submits additional manufacturing controls information.

Supporting Documents: See Chem. Rev. #1.

Remarks:
Chem. Rev. #2 dated 12-4-89 found manufacturing contrtols information approvable. Some modifications of the alt. assay and content uniformity methods were still necessery before these methods could be accepted for regulatoy use.

The 1-29-90 amendment is in response to our reqùests made during that meeting.

Conclusion and Recommendation:

The application is now approvable from the chemist's standpoint.

/S/

Helmut B. Nunn
Review Chemist

cc: NDA Orig.
HFD-510
HFD-510/HNunn

R/D initialed by
Wang 1350c

6-21-90

D6

AUG 6 1996

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 19-781 Chem.Review #: 4 Review Date: 8/2/96

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	9/30/87 by Besins Pharmaceuticals		
RESUBMITTED	3/17/89 by LaSalle Laboratories		
RESUBMITTED	2/8/96 by Schering Corporation	2/9/96	4/5/96
AMENDMENT	6/21/96	6/21/96	6/26/96

NAME & ADDRESS OF APPLICANT: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

DRUG PRODUCT NAME:

Proprietary:	Prometrium Capsules
Nonprooprietary:	Progesterone Capsules
Code Name/#:	Sch 961
Chem.Type/Ther.Class:	3 S

PHARMACOL.CATEGORY/INDICATION: Secondary amenorrhea

DOSAGE FORM: Soft gelatin capsules

STRENGTHS: 100 mg

ROUTE OF ADMINISTRATION: Oral

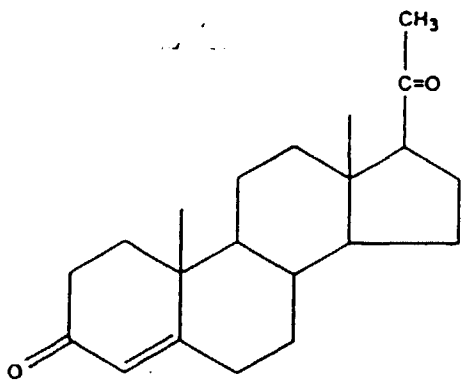
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

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

Molecular Formula: $C_{21}H_{30}O_2$

Molecular Weight: 314.47



SUPPORTING DOCUMENTS: IND

DMF
DMF
DMF
DMF
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DMF
DMF
DMF

An authorization letter from each DMF holder was included.

REMARKS:

The original application was submitted 9/30/87 by Besins Pharmaceuticals and a "Refusal to File" letter issued 12/1/87. Besins Pharaceuticals was dissolved 9/26/88. The application was resubmitted 3/17/89 by LaSalle Laboratories, US affiliate of Besins-Iscovesco Pharmaceuticals, Inc. The 3/17/89 resubmission incorporated by reference the entire original submission of 9/30/87. Ownership of the NDA was transferred to Schering Corporation on 7/1/90. A Not Approvable letter was sent to Schering on 8/17/90. As resubmitted, the application, which contains a complete CMC section, still provides for as the drug substance manufacturer, and as the drug product manufacturer. The tradename of the product has been changed from Utrogestan Capsules to Prometrium Capsules.
The amendment dated 6/21/96 contained replacement pages describing the "Sites of Manufacturing, Packaging and Control Operations" for the drug substance and the drug product.

CONSULTS: EER sent 2/21/96. Facilities reported acceptable 7/8/96.

CONCLUSIONS:

The application is satisfactory with regard to chemistry, manufacturing and controls, except that, from the chemistry viewpoint, minor changes are required in the These changes are specified in the (Item H.). The completed EER (dated 08-Jul-96) states that all facilities are acceptable. The application can therefore be approved (for CMC) after the labeling changes are made. The approval letter should and should inform the applicant that their cooperation expected.

/S/

Patricia Stewart
Review Chemist, HFD-510

MAY 8 1998

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)
REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS

NDA # 19-781 **Chemistry Review** # 5 **Review Date**: 5-6-98

SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
Amendment	5-1-98	5-4-98	5-4-98
Amendment	7-25-97	7-31-97	7-31-97

NAME AND ADDRESS OF APPLICANT
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

DRUG PRODUCT NAME
Proprietary: Prometrium^{R}
Non-proprietary/USAN: Progesterone, USP Capsules
Compendium: does not apply
Code name/number:None
Chem. Type/Ther. Class: 3 S

ANDA SUITABILITY PETITION/DESI/PATENT STATUS:
N/A
PHARMACOL. CATEGORY/INDICATION: Prometrium^{R} is indicated for prevention of secondary amenorrhea

DOSAGE FORM: Capsules
STRENGTHS: 100 mg capsules

ROUTE OF ADMINISTRATION: Oral

DISPENSED: By prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:
Pregn-4-ene-3,20-dione
$C_{21}H_{30}O_2$, Molecular Weight: 314.47

SUPPORTING DOCUMENTS: DMF Type

RELATED DOCUMENTS
20-841

CONSULTS

The Tradename was sent to the Labeling and Nomenclature Committee on May 6, 1998.

REMARKS/COMMENTS

The amendment dated May 1, 1998 was submitted for final draft labeling. The amendment dated July 25, 1997 was submitted for additional stability data to fulfill the commitment made in earlier amendment dated February 6, 1996

The NDA 19-781 is indicated for secondary amenorrhea. The updated stability data was reviewed and found satisfactory.

. The same formulation is used in NDA 19-781.

CONCLUSION AND RECOMMENDATIONS

The application was deemed approvable pending changes in labeling. Satisfactory changes in the labeling have been made and the application can be approved with respect to CMC.

/S/

Amit K. Mitra, Ph.D

cc: NDA original
HFD-580/A. K. Mitra, Ph.D/ 5-6-98
HFD-580/M. J. Rhee, Ph.D
HFD-580/D. Moore
R/D. Init. By- 5/8/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PROMETRIUM CAPSULES

PROGESTERONE CAPSULES

SOFT GELATIN CAPSULES

NDA 19-781

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF REPRODUCTIVE & UROLOGIC DRUG PRODUCTS
(HFD-580)

FINDING OF NO SIGNIFICANT IMPACT

NDA 19-781

Prometrium Capsules

Progesterone Capsules

Soft Gelatin Capsules

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Prometrium (Progesterone USP, Micronized), Schering-Plough Corporation has prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Progesterone is a chemically synthesized drug which is administered in soft gelatin capsules for secondary amenorrhea. The drug substance will be manufactured by *(Classified as confidential)* at a foreign site. The drug product will be manufactured by ~~*(Classified as confidential)*~~ See Fish Attachment at a U.S. site. For the foreign site of manufacture, appropriate environmental compliance certification is included (Classified as confidential). The finished drug product will be used by consumers throughout the United States.

Progesterone is almost completely metabolized and excreted from the body as a very large number of oxidized and/or reduced products, the majority of which are in conjugate form (glucuronides and sulfates). Approximately 14% of administered Progesterone is generally recovered in the urine as conjugated pregnanediol. Any excreted metabolites will enter public water and sewer treatment facilities and will have no known effect on the environment. Any manufacturing waste entering the environment is expected to be rapidly biodegraded by soil and water microbial organisms.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed disposal facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

/S/

7/22/96
DATE

PREPARED BY
Patricia M. Stewart
Chemist
Division of Metabolic & Endocrine Drug Products

/S/

7/26/96
DATE

DIVISION CONCURRENCE
Helen W. Davies
Chemistry Team Leader
HFD-820 assigned to HFD-580

/S/

8/1/96
DATE

CONCURRED
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)
EA submitted by Applicant
FDA Addendum

Orig. NDA 19-781
HFD-580/Division File
HFD-510/Chem/PStewart
HFD-580/CSO/CKish
HFD-004/FONSI File/NDA 19-781
HFD-004/Docket File
HFD-019/FOI COPY

1. DATE: January 29, 1996

2. NAME OF APPLICANT: Schering-Plough Corporation

3. ADDRESS: 2000 Galloping Hill Road
Kenilworth, New Jersey 07033

4. DESCRIPTION OF THE PROPOSED ACTION:

a. Requested Approval

Schering-Plough Corporation is submitting an Environmental Assessment (EA) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prometrium Capsules. The drug product is formulated with 100 mg/capsule of Progesterone USP, Micronized. Prometrium Capsules will be packaged in plastic bottles or blister packaging. An EA is being submitted pursuant to 21 CFR Part 25.31a(a).

b. Need for Action

Prometrium Capsules are indicated for secondary amenorrhea in women.

c. Production Locations

The drug substance, Progesterone, will be manufactured for the applicant by Contract Manufacturer #1 at a foreign site.

The drug product, Prometrium Capsules, will be manufactured for the applicant by Contract Manufacturer #2 at a U.S. site.

For the foreign site of manufacture, appropriate environmental compliance certification is included in **Confidential Appendix 3.**

For the U.S. site for Contract Manufacturer #2, the facility is located on a 30-acre site in an industrial/commericial area. Operations and activities at the site include manufacturing, warehousing, research and development, offices, and supporting activities. The facility is located in a coastal region of the United States where the climate is subtropical.

d. Locations of Use

Through the approval of this action, Prometrium Capsules will be used by consumers throughout the United States.

e. Disposal Sites

See EA format item 6.b for a description of the disposal of returned, expired or rejected drug product.

Any drug product not used by consumers will be disposed of by users in their homes or at hospitals, pharmacies or medical clinics in the U.S. according to procedures set at those facilities. Typically these procedures result in the disposal of waste via a community's solid waste management system which may include landfills, incineration, and recycling, although users may dispose of minimal quanitities of unused drug in the sewer system.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

a. Nomenclature

i. Established Name: Progesterone

ii. Brand/Proprietary Name: N/A

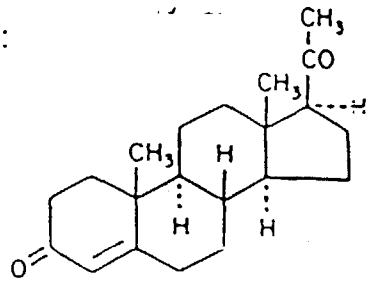
iii. Chemical Name: Pregn-4-ene-3,20-dione

b. CAS Registration #: 57-83-0

c. Molecular formula: $C_{21}H_{30}O_2$

d. Molecular weight: 314.47

e. Structural Formula:



f. **Physical Description**: white, crystalline powder that is odorless and commonly available in two polymorphic forms, alpha and beta. This product is formulated only with the alpha form.

g. **Additives**:

In addition to the drug substance, the final dosage form consists of the following ingredients:

Substance	CAS #
Peanut Oil	8002-03-7
Lecithin	8002-43-5
Gelatin	9000-70-8
Glycerin	56-81-7
Titanium Dioxide	13463-67-7
Dye FD&C Red No. 40	25956-17-6
Dye D&C Yellow No. 10	68814-04-0

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

SITE OF MANUFACTURE OF THE DRUG SUBSTANCE

Environmental compliance for the manufacture of the drug active by Contract Manufacturer #1 as a foreign site is addressed through appropriate certification included in **Confidential Appendix 3.**

SITE OF MANUFACTURE OF DRUG PRODUCT

The manufacture of Prometrium Capsules at Contract Manufacturer #2's U.S. site is addressed by the following:

a. Substances Expected to be Emitted

This information is provided in Confidential Appendix 2.

b. Controls Exercised

i. Air

During the manufacture of Prometrium Capsules, air emissions occur which are regulated via a limit on volatile organic compounds (VOC's) in the site's air permit.

Air exhausts from the drying process are controlled via a vapor recovery unit. The unit consists of carbon adsorption beds with two beds typically used for active adsorption while one is being regenerated. During regeneration, VOC's are desorbed with steam, condensed, and purified by distillation for reuse in the manufacturing process. The vapor recovery system has an approximate unit efficiency of 90%.

ii. Wastewater

Wastewaters are generated as a result of cleaning vessels and other process equipment during the manufacture of Prometrium Capsules. The wastewater is discharged to the municipal sewer system for treatment at the local Publicly Owned Treatment Works (POTW).

iii. Solids

During manufacture of the drug product, solid waste is generated as rejected product and scrap material.

The manufacturing facility collects this solid waste material for off-site disposal. A licensed disposal company is used to transport the waste to an approved disposal facility. Authorized disposal facilities such as the local county solid waste management facility and other solid waste disposal facilities are used by the site. The identification and permit information for two facilities typically used are provided in Confidential Appendix 2. Solid waste is incinerated as a final disposal measure.

Returned goods will be collected at the applicant's facility in Kenilworth, New Jersey. This material is typically sent to an authorized disposal facility for high temperature incineration. The identification and permit information regarding a facility typically used is provided in Confidential Appendix 2.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Listed below are the laws, codes, and rules at the Federal, State, and local level that regulate emissions including occupational requirements and are applicable to the Contract Manufacturer #2's U.S. site:

* National Primary and Secondary Air Quality Standards (40 CFR 50).
* National Emission Standards for Hazardous Air Pollutants (40 CFR 61).
* Statutes for State of Florida, Chapter 403.
* Florida Administrative Code Rules 17-2 & 17-4.
* County Ordinance No. 89-70, Subpart 6.620 as amended by 90-63.
* U.S. EPA Pretreatment Regulations (40 CFR 403).
* U.S. EPA Effluent Guidelines and Standards for Pharmaceuticals Manufacturing (40 CFR 439).
* City Ordinance No. 86-45.
* Resource Conservation and Recovery Act of 1976 PL 94-580 as amended
* Florida Solid and Hazardous Waste Management Act, Florida Statutes Annotated Title 29, Chapter 403 enacted by Laws of 1974 Chapter 342 as amended.
* U.S. Dept. of Labor, Occupational Safety and Health Administration (OSHA), Occupational Safety and Health Standards (29 CFR 1910)

The following table lists permits that are applicable to the control of emissions from the Contract Manufacturer #2's U.S. site:

Emission	Authorizing Agency	Permit #	Exp. Date
Air	Florida Dept. of Env Protection	AO52-201625	11/15/96
Waste-water	City Dept. of Public Works	950920-RLS4302C	9/19/96

Contract Manufacturer #2's U.S. site is in compliance with all emission requirements including occupational which are applicable to the manufacturing operations.

Material Safety Data Sheets (MSDS's) for the drug substance is provided in Non-Confidential Appendix 1.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The approval of the proposed action and subsequent increase in production will not affect compliance with current emission requirements. Using the estimated fifth year production volume, the Contract Manufacturer #2's U.S. facility will meet air emission limits and wastewater permit requirements considering the additional production at the site.

e. Expected Introduction Concentrations

Introduction concentrations are provided for the drug substance, Progesterone.

i. Expected Introduction Concentrations from Use

The FDA regulations, 21 CFR Part 25.31(a)(7), require a prediction of the environmental concentrations of substances entering the environment as a result of the use of the product. The information below provides an estimate of the expected introduction concentration (EIC) of the drug substance for the aquatic environmental compartment. The concentration is based on the consumption of the drug product by users in the United States and disposal of the substance after use to wastewater collection systems and thereafter to wastewater treatment plants for treatment.

The EIC in the environment as a result of drug product use across the U.S. is estimated to be:

EIC - Aquatic for Progesterone = 5.3×10^{-4} ppm (or 0.5 ppb)

7. FATE OF EMITTED SUBSTANCES:

Based on the Tier 0 approach under the new FDA Guidance for the submission of EA's, format item 7 is not normally needed if the expected environmental concentration due to entry into the environment is less than 1 ppb.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

Based on the Tier 0 approach under the new FDA Guidance for the submission of EA's, format item 8 is not normally needed if the expected environmental concentration due to entry into the environment is less than 1 ppb.

9. USE OF RESOURCES AND ENERGY:

Based on the Tier 0 approach under the new FDA Guidance for the submission of EA's, format item 9 is not normally needed if the expected environmental concentration due to entry into the environment is less than 1 ppb.

10. MITIGATION MEASURES:

Based on the Tier 0 approach under the new FDA Guidance for the submission of EA's, format item 10 is not normally needed if the expected environmental concentration due to entry into the environment is less than 1 ppb.

11. ALTERNATIVES TO THE PROPOSED ACTION:

Based on the Tier 0 approach under the new FDA Guidance for the submission of EA's, format item 11 is not normally needed if the expected environmental concentration due to entry into the environment is less than 1 ppb.

12. LIST OF PREPARERS:

This document was compiled by Charles Kreider, Environmental Engineer (BS, Villanova University, 1985), for Schering-Plough Corporation.

In addition to the preparer, the following individuals were involved in the preparation of this environmental assessment:

Schering Laboratories

Mr. Scott Gordon, P.E.	Director, Environmental Regulatory Affairs & Program Development

Mr. Keith W. Tingberg	Senior Environmental Engineer, Environmental Regulatory Affairs & Program Development
Ms. Lynne M. Fredericks	Marketing Research

Schering-Plough Research Institute

Dr. Nicholas DeAngelis, Ph.D.	Director of Pharmaceutical, Analytical, and Chemistry Research and Development
Dr. Bruce McCullough, Ph.D.	Director of Toxicology
Dr. Nicola Zampaglione, Ph.D.	Drug Metabolism

13. CERTIFICATION:

The undersigned officials certify that the information presented is true, accurate and complete to the best of their knowledge of Schering-Plough Corporation.

The undersigned officials acknowledge that the EA document and Appendix 1 are non-confidential in nature and understand that this information will be made available to the public in accordance with CFR 1506.6.

Appendices 2 and 3 of this document contain information which is considered confidential in nature and is therefore not releaseable to the public.

DATE: January 29, 1996 BY: _____
Charles Kreider
Environmental Engineer
Schering Laboratories

DATE: 1/29/96 BY: _____
Joseph A. Nusser, P.E., Senior Director
Environmental Projects & Compliance
Schering Laboratories

14. APPENDICES:

Appendix 1 - Material Safety Data Sheet (MSDS) for Progesterone, March 5, 1993.

Appendix 2 - *Confidential Business Information* as referenced in the EA document

Appendix 3 - *Confidential Information regarding* Certification for Contract Manufacturer #1 foreign site

APPENDIX 1

MSDS Information for Progesterone

MATERIAL SAFETY DATA SHEET

no. 93.412

SECTION I

CHEMICAL NAME AND SYNONYMS:	Pregn-4-ene-3,20-dione. Pregnenedione. Progesteronum.
CAS NO.:	57-83-0 FORMULA: $C_{21}H_{30}O_2$
COMMON NAME:	PROGESTERONE

SECTION II - HAZARDOUS INGREDIENTS

MATERIAL/COMPOSITION:	Not applicable.	NATURE OF HAZARD:	Not applicable.

SECTION III - PHYSICAL DATA

MELTING POINT:	120 - 130 °C.	SPECIFIC GRAVITY:	Not applicable.
SOLUBILITY IN WATER:	Insoluble.	BOILING POINT:	Not applicable.
VAPOUR PRESSURE (mm Hg):	Not applicable.	VOLATILE BY VOLUME %:	Not applicable.
VAPOUR DENSITY (AIR = 1):	Not applicable.	EVAPORATION RATE:	Not applicable.
APPEARANCE AND ODOUR:	White to almost white or colourless crystals or crystalline powder. Odourless.		

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

FLAMMABLE LIMITS:	LOWER: Not applicable. UPPER: Not applicable.
FLASH POINT (method used):	Not applicable.
FIRE EXTINGUISHING MEDIA:	Water, extinguishing powder, carbon dioxide or foam.
SPECIAL FIRE FIGHTING PROCEDURES:	Evacuate personnel to safe area. Fire-fighters should use self-contained breathing equipment and protective clothing.
UNUSUAL FIRE AND EXPLOSION HAZARDS:	Ground mechanical equipment in contact with dry material to dissipate the potential build up of static electricity as prevention against dust explosion.

SECTION V - HEALTH HAZARD DATA

THERAPEUTICAL CATEGORY:	Progestogen.	THRESHOLD LIMIT VALUE:	None established.

HAZARDS: **Routes of exposure:** Inhalation, skin absorption, mucous membrane absorption, ingestion. **Effects of over-exposure:** In general: Possible adverse effects of progestogens in general; Acute effects: Harmful if swallowed, inhaled or absorbed through skin. May cause irritation; May cause tenderness of the breasts; Effects on menstruation and fertility; Exposure can cause suppression of adrenal gland secretion, hyperglycaemia, Cushing's syndrome, water retention, electrolyte imbalance, acne, weight gain, gastro-intestinal effects, carpal tunnel syndrome, alopecia and deep vein thrombophlebitis. LDLo (ipr-rat): 327 mg/kg, LDLo (ivn-mouse): 100 mg/kg. Chronic effects: Possible carcinogen (IARC: Animal sufficient evidence; overall evaluation of the group progestogens: 2B). An experimental carcinogen, neoplastigen, tumorigen and teratogen; Experimental and human reproductive effects; Human teratogenic effects; Mutagenic data; Possible risk of irriversible effects; Long term exposure may cause reversible gynaecomastia in male and effects on menstruation and fertility. Additional: May cause sensitization by inhalation and skin contact.

SECTION V - HEALTH HAZARD DATA (continued)

FIRST AID PROCEDURES:	Inhalation	: Remove from exposure, fresh air, rest. If breathing is difficult give oxygen. If not breathing give artificial respiration. Call a physician (show this Material Safety Data Sheet).
	Skin	: Flush with copious amounts of water while removing contaminated clothing and shoes. Wash contaminated clothing before reuse.
	Eyes	: Flush with copious amounts of water for at least 15 minutes, separating eyelids with fingers.
	Ingestion	: Wash out mouth with water provided person is conscious. Call a physician (show this Material Safety Data Sheet).

SECTION VI - REACTIVITY DATA

STABILITY:	The product is stable.	CONDITIONS TO AVOID:	Not applicable.
INCOMPATIBILITY (Materials to avoid):		None.	
HAZARDOUS DECOMPOSITION PRODUCTS:		None.	
HAZARDOUS POLYMERIZATION:	Will not occur.	CONDITIONS TO AVOID:	Not applicable.

SECTION VII - SPILL OR LEAK PROCEDURES

SPILLS:	Vacuum or sweep up spillage and transfer into an appropriate container for waste disposal. Avoid dust. Ventilate area and wash spill site.
DISPOSAL:	Disposal on chemical waste dump site or by incineration according to Federal-, State- or local laws.

SECTION VIII - SPECIAL PROTECTION

RESPIRATORY PROTECTION:	Dustmask e.g. 3M no. 8710.		
VENTILATION:	LOCAL: Yes GENERAL: Yes (Mechanical)	SPECIAL: Not applicable. OTHER: Not applicable.	
PROTECTIVE GLOVES:	Chemically compatible.	EYE PROTECTION:	Goggles.
OTHER PROTECTIVE EQUIPMENT:	Wear a clean well fitted and closed overall. Change daily.		

SECTION IX - STORAGE CONDITIONS, HANDLING PRECAUTIONS

HANDLING AND STORING:	Eating, drinking or smoking near material is forbidden. Store at 15 to 25 °C in well closed containers protected from light and moisture. Avoid contact with eyes, skin or clothing. Avoid breathing of dust. In case of skin contact showering is necessary with lots of water and soap. Avoid exposure to women especially during pregnancy and lactation. When grinding or micronising material a supplied air respirator (hood fit type) has to be used.

SECTION X - ADDITIONAL INFORMATION

Toxicity data: RTECSno: TW0175000, N.I. SAX et al. (7 ED), 1989, p 1411. IARC Monographs, Volume 50, (1990), p 38. IARC Monographs Suppl. 7, (1987).

The information contained in this document is to our best knowledge true and accurate but all data, instructions, recommendations and/or suggestions are made without guarantee.

THIS SHEET SUPERSEDES MSDS NO. 87.151 DATED: July 21, 1987

DATE ISSUED 3/5/93 SIGNATURE

FDA ADDENDUM

In a separate communication to CDER, the applicant authorized release of the name of the drug product manufacturer identified as contract manufacturer #2 in the EA.

ENVIRONMENTAL ASSESSMENT

1. Date: September 11, 1987

2. Name of Applicant:

Besins Pharmaceuticals, Inc.

3. Address:

1333 New Hampshire Ave. N.W.
Suite 400
Washington, DC 10036

4. Description of Proposed Action:

The proposed action is the approval of a New Drug Application (NDA) for Utrogestan^{tm} (micronized progesterone) capsules. Utrogestan will be manufactured by:

The product will be marketed and consumed nationally. The environment adjacent to the manufacturing site is that typical of a small industrial park.

5. Identification of chemical substances that are the subject of the proposed action:

Utrogestan contains the following ingredients:

Progesterone ($C_{21}H_{30}O_2$), CAS Reg. No. 57-83-0
Peanut Oil, CAS Reg. No. 8002-03-7
Lecithin, CAS Reg. No. 8002-43-5
Gelatin, CAS Reg. No. 9000-70-8
Glycerin ($C_3H_8O_3$), CAS Reg. No. 56-81-5
Titanium Dioxide (TiO_2), CAS Reg. No. 13463-67-7
FD&C Red #40, CAS Reg. No. 25956-17-6
D&C Yellow #10, CAS Reg. No. 8004-92-0

The following substances are used and removed during the manufacture of Utrogestan:

6. Introduction of substances into the environment

During the manufacture of Utrogestan, there will not be any substances emitted to the environment. The

mixture will be collected and properly disposed of in accordance with all Federal, State and local requirements.

Items 7-11, 14 and 15 not required.

12. List of preparers

Guidelines, Inc.
18441 N.W. 2nd ~~Avenue~~
Miami, Florida 33169

13. Certification

I certify that, to the best of our knowledge, the information presented is true, accurate and complete.

Michael K. Powell
President

9/28/87
Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

PHARMACOLOGY REVIEW(S)

NDA 19-781 ORIGINAL 11 August 1989

La Salle Laboratories
c/o Akin, Gump, Strauss, Hauer & Feld
1333 New Hampshire Ave., N.W., Suite 400
Washington, D.C. 20036

AUG 11 1989

Submission: 20 March 1989

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Resubmission dtd. 17 March 1989

Utrogestan (progesterone, USP) capsules - 100 mg

Progestin — Micronized progesterone

Indications: Secondary amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

Related: IND

DMF DMF

Manufactured by:

Chemical Name: pregn-4-ene-3,20-dione

Composition: Each peach-colored, opaque, soft gelatin capsule contains 100 mg micronized progesterone for oral administration. Inactive ingredients are peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow #10, and FD&C red #40. Particle size: Less than microns - % minimum; Less than microns - % minimum; Less than microns - % minimum.

Dosage and Administration: Secondary Amenorrhea - Utrogestan (progesterone, USP) Capsules may be given in daily oral dosages of 200 to 300 mg at bedtime for from 5 to 10 days. A dose for inducing an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen is 300 mg of Utrogestan Capsules daily for 10 days. In cases of secondary amenorrhea, therapy may be started at any time. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing therapy with Utrogestan.

Abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology - Beginning on the calculated 16th or 21st day of the menstrual cycle, 200 to 300 mg of Utrogestan Capsules may be given daily at bedtime for from 5 to 10 days. To produce optimum secretory transformation of an endometrium that has been adequately primed with

either endogenous or exogenous estrogen, 200 to 300 mg of Utrogestan Capsules daily at bedtime for 10 days beginning on the 16th day of the cycle is suggested. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing therapy with Utrogestan. Patients with a past history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with Utrogestan.

Foreign Preclinical Data: Yes - France, Italy and Great Britain. See individual studies.

Preclinical Studies:

Pharmacological Effects of Micronized and Crystallized Progesterone Administered Orally in an Aqueous Suspension; Comparison with the Action of Progesterone Administered Subcutaneously:

The effects of progesterone were evaluated by measuring the increase of uterine weight and endometrial development Test) in the impuberal female New Zealand rabbit treated with estradiol (0.5 µg x 6) and by studying formation of a deciduoma in the castrated female Sprague-Dawley EOPS rat pretreated with estradiol (1 µg x 4) and after local traumatism of the uterus. (The healthy uterine horn pretreated with estradiol shows no response to effects of progesterone. After traumatization to provoke formation of deciduoma, progesterone exerts a trophic or edematous reaction in animals pretreated with estradiol.)

Rabbit (daily x 5): Oral - 5, 10, 25, 50, 100 mg aqueous suspension (1% carboxymethylcellulose) of micronized (5µ) progesterone; oral - 50 and 100 mg aqueous suspension of non-micronized progesterone; s.c. - 0.03, 0.1, 0.3 mg oily (sesame seed) solution of progesterone.

Increases in rabbit uterine weight and endometrial development are dependent on the log dose. The micronized progesterone preparation was 220-250 times less active in uterine weight increase and endometrial development than the s.c. injection. It was twice as active in increasing uterine weight and 4-5 times more active in development of the endometrium than the crystallized preparation.

Rat (daily x 8): Oral micronized (5µ) aqueous suspension of progesterone - 25, 50, 100, 200, 500 mg; Oral crystallized aqueous suspension - 100, 500 mg; s.c. 0.25, 0.5, 1, 2 mg oily (Peanut) solution of progesterone.

In the rat an increase of damaged uterus and decidual response was only seen after 2 mg/day s.c. The oral micronized preparation significantly increased damaged uterus weight at doses of 100 and 200 mg/day. No decidual response was provoked even at the highest dose. The crystallized form showed no effect on damaged uterus weight and caused no decidual reaction at 500 mg/day. It is reported that out of 6 animals in the 500 mg/day micronized progesterone group 3 died after the first and 3 after the second dose. Deaths were preceded by drowsiness. One out of six died after the second 200

mg dose and one after the second 50(?) mg dose. Table II also shows deaths for one 100 mg and two 500 mg normal progesterone also one estradiol control and one 0.5 mg s.c. progesterone.

Plasma Concentration Kinetics of Oral or Subcutaneous Progesterone Administered to the Oophorectomized Female Rat.

An oily (peanut) suspension (2:1) of progesterone was tested in rats 4-5 weeks after oophorectomy. ^{3}H doses of micronized (mean particle size 5μ) progesterone were 125, 250 and 500 mg/kg orally and 1.25, 2.5 and 5 mg/kg subcutaneously. Blood samples were obtained at 0.5, 1, 2, 4, 8 and 24 hrs. The rats were sacrificed after 24 hrs.

Oral administration: A depressive state was seen with the two higher doses which, when added to the anesthesia, led to considerable mortality in the first 8 hours. A blood/dose radioactivity relationship was evident after 24 hours. No significant differences were noted before that time. Total radioactivity was dose related with highest values being found in the liver followed by kidney, uterus and muscles. During the first hour, plasma progesterone represented only a fraction of the total radioactivity. The percentage was about 10% the first hour, 5-6% the 4th hour and 2.5% at 24 hours. Plasma progesterone (not dose dependent) was maintained at about μg/g during 24 hrs. with the 125 mg/kg dose. It reached a maximum at 8 hrs. μg/g) with the 250 mg/kg dose and at 24 hrs. (32 μg/g) with the 500 mg/kg dose.

S.C. administration: Following the 1.25 mg/kg dose, plasma radioactivity reached a plateau after one hour and was maintained in the range of 50 ng/g for 8 hours. At 24 hours the value was about doubled. The 2.5 and 5.0 mg/kg doses showed larger values with somewhat similar kinetics. Total radioactivity was dose dependent with the order of organ activity similar to the oral preparation. The plasma progesterone concentration was proportional to the dose with a maximum concentration being reached 0.5-1 hr. post dose. Prior to the 24th hour progesterone represented a greater fraction of radioactivity than that following oral administration. Percentages were greater than 15% the first hour, about 12% the 4th hour and 1.5-2% after 24 hours.

Metabolites: Dihydroxyprogesterone (DHP) - Following both routes concentrations were % the first hour decreasing to % by 8 hours. DHP represented % after s.c. and % (15% at the 4th hour) following oral administration.

Delta 4-pregnan-20 alpha ol-3-one (delta-4) - Following the 125 mg/kg oral dose the percentage of delta-4 decreased from % the 1st hr. to % after 8 hrs. For 250 and 500 mg/kg it was about % at 1-2 hrs. and %

at 8 hours. The percentage of delta-4 at 1 hr. following s.c. administration remained fairly constant at about 10% for 4 hrs. and then began to decrease. Following low dose oral administration delta-4 represents of the plasma progesterone concentration after 2 hours. With the higher doses the delta-4/progesterone ratio was at 1 hour. Following s.c. administration delta-4 is less than progesterone during the first hour, similar at the 2nd hour and greater than progesterone at the 4th and 8th hours.

Acute Toxicity:

Rats: "Acute median lethal oral dose"
(Food was withheld overnight before treatment.)
Males - 1000-2000 mg/kg
Females - 320-400 mg/kg

Signs included: reduced rate of activity and reduced or increased respiration leading to collapse, often with body tremors, and a comatose state, and death.

28-Day Subacute Oral Toxicity of Micronized Progesterone in Charles River CD Rats:

Treatment began 21 July 1977.

Dose: 0, 40, 100, 250 mg/kg Progesterone, Micronized, was administered in peanut (arachis) oil once each day 7 days/week for 28 days.

No. Animals: 5M:5F Charles River CD Rats/group, 7 weeks of age.

Results:
Mortality: None
Clinical Signs: 40 mg/kg - no signs of treatment reaction.
100 mg/kg - some salivation after dosing on a number of occasions.
250 mg/kg - salivation, reduced activity, collapse frequently associated with an increased rate of respiration; or coma from the second treatment onwards. Each rat showed all of the above on different occasions within 1-3 hrs. of treatment on between 11 and 23 days.
Bodyweight: Males - no apparent treatment related effect. Females - increased growth rate compared to controls. Statistically significant for 100 and 250 mg/kg.
Food Intake: Males - treated showed a small reduction in intake. Females - treated showed a more marked dose-related increase .

Efficiency of Food Utilization: Males - no treatment related effect. Females - treated reportedly showed a marginal increase in the overall efficiency of food utilization.

Hematology, Clinical Chemistry, Urinalysis: Not given.

Organ Weights: (adrenal glands, kidneys, liver, ovaries, testes, spleen) Liver - weight increase in high dose females. Other small differences in female spleen, kidney and gonads were not considered by the sponsor to be related to treatment.

Macroscopic Pathology: No treatment related effects. Incidental - Unilateral hydronephrosis in 1 control and 1 on 40 mg/kg; small testes in one 100 mg/kg rat.

Histopathology: (Tissues saved and preserved but only liver examined.) Reported that treatment related morphological changes were not apparent in liver sections examined.

12-Week Subacute Oral Toxicity of Micronized Progesterone in Female Sprague-Dawley Rats.

Study began 6/16/1978.

Dose: 135, 45, 15, 5, 0 (Groups I-V) mg/kg Progesterone, Micronized suspended in peanut oil. 12 weeks orally by gavage.

No. Animals: 18 female rats per group.

Results:

Mortality: 1 high dose rat due to gavage.

Clinical Signs: Sedation and relaxation were seen with the high dose the first week.

Body Weight and Food Consumption: No apparent treatment effect.

Hematology: Hematocrit of treated slightly lower than controls.

Clinical Chemistry: Compared to controls dose related decreases were reported for Total Protein, Albumin, and Cholesterol and dose related increases for LDH, Cl^-, and Ca^{++}. (Mean Protein and albumin values of the 45 mg/kg group were comparable with controls.) Significance was mainly at the high dose. Decreases in CO_2, Inorganic Phosphorus, Glucose and Na^+ were reported as occasional and not dose-related. A significant increase was reported for Total Bilirubin for the high dose and a significant decrease for the 15 mg/kg dose.

Urinalysis: pH - increased at lower doses and decreased at the high dose.

Organ Weights: Absolute pituitary weights were statistically lower than controls for the 135, 45, 5 mg/kg groups and higher than controls for the 15 mg/kg group. The liver weights of the high dose group were also significantly lower than that of the control group. Although not significant, findings showed a similar trend for the relative pituitary and liver weights. In general a number of the mean organ weights of the 15 mg/kg group appear to be less than that of controls. It is reported that the mammary glands of the 15 mg/kg group are statistically lower than controls (this organ not listed in data table).

Gross Pathology: 1 high dose - lobe of liver of hard consistency with loss of hepatic structure. One of 15 mg/kg group also had a yellowish colored liver. One control had left kidney hydronephrosis.

Histopathology: (Groups I, II, V) No apparent drug related findings. Both treated and controls showed some lung inflammations. Hepatic lesion in one high dose (necrosis of hepatic parenchyma with hemorrhagic foci) thought to be of infective origin.

12-Week Subacute Oral Toxicity Study of Micronized Progesterone in Female Beagle Dogs.

Start of treatment: 22 Aug 1978.

Dose: 325, 125, 50, 0 (Groups I-IV) mg/kg micronized Progesterone suspended in peanut oil and incorporated in a ball of meat for daily oral administration.

No. Animals: 4 female Beagle Dogs per group. 7-9 mos. of age. 7-10 kg.

Results:

Mortality: None

Clinical Signs: Signs of sedation immediately after treatment at the highest dose for the first 30 days. The same animals showed a state of irritation during the entire period.

Bodyweight: Not influenced by treatment.

Food Consumption: No variation between treated and controls.

Hematology: 0, 45 days, 3 mos. (incl. protein & lipoprotein electrophoresis) Various mean parameters were reported to be significantly different between the groups at the various time periods.

Initially:

Higher - mid dose hematocrit (all treated greater than controls); high dose % alfa$_2$ globulin;

Lower - high dose % eosinophils (treated less than controls). mid and low dose % beta-globulin.

45-Days:

Higher - high dose leukocytes; mid dose prebeta and high dose beta lipoprotein (treated of both parameters greater than controls); mid and high dose % alpha$_2$ globulin;

Lower - mid dose % eosinophils; mid dose % alpha$_1$ globulin; mid and low dose % gamma globulin; mid and high dose % alpha lipoprotein.

3 months:

Higher - mid dose lymphocytes; low dose methemoglobin; mid and high dose % alfa$_2$ globulin; mid and low dose % prebeta lipoprotein.

Lower - mid dose % neutrophils; low dose leukocytes; mid and low dose % alfa lipoprotein.

Blood Chemistry: 0, 45 days, 3 mos.

Significant variations were reported for the following parameters:

Initially:

Lower - high dose electrolytes (Cl^-, Na^+, K^+, and Ca^{++})

45-Days:

Modifications correlated with dose were reported:

Increase - CO_2 (mid dose sig.); total cholesterol (all treated doses sig.); BUN (not sig.); Ca^{++} (high dose sig.)

Decrease - High doses significant for SGPT, Cl^-, Na^+, and K^+ (K^+ mid dose also sig.).

3 months:

Increase - Total cholesterol, total lipids (high dose not sig.), BSP (low dose only sig.) of all treated groups; BUN (low dose only sig.; mid dose less than control); Na^+ mid dose sig.;

Decrease - SGPT high dose significant.

Urinalysis: Findings in general comparable with controls. Some RBCs - comparable with controls and reported as due to bladder inflammation.

Gross Pathology:

Lungs - small nodules seen at random in 7 dogs in treated and control groups.

Kidney - wrinkled surface in one high dose. Similar but less pronounced findings were seen in one mid dose, one low dose and one control.

Mesenteric lymph nodes - one high dose dog had an inflammation; its Caecum also showed signs of inflammation with necrotic patches.

Urinary bladder - inflammation in two mid dose animals.

Uterine horns - thickening seen in two high dose one mid dose and one low dose.

Ovaries - one high dose and one mid dose had small cysts.

Pituitary - cyst in one mid dose.

Mammary gland - one high dose had nodules (left distal gland) containing a caseous liquid.

Histopathology:

Rathke's pouch - Cyst in 2 high dose, one mid dose and one low dose.

Foci of Pneumonia - one high dose, one mid dose, one low dose and 2 controls.

Breast - adenosic disease - one high dose.

Endometrium - one high dose adenocystic dysplasia; one mid dose cystic dysplasia.

Lymph nodes - one high dose hemorrhagic.

Ovary - one mid dose follicular cyst.

Note: Reported that for technical reasons unable to perform T=0 functional tests: hepatic and renal, lipoprotein electrophoresis, prothrombin time, and triglycerides.

Labeling: Contains no preclinical pharmacology. See comments section p. 10.

Comments and Conclusion:

Utrogestan, micronized progesterone capsules, is an oral dosage form which is chemically identical to progesterone of ovarian origin. Although progesterone is a naturally occurring steroidal compound, it is usually not effective orally because of poor bioavailability and the rapid metabolism in the intestinal epithelium and liver. Micronization of progesterone appears to permit an increased efficiency of its oral absorption and thus circumvents the more difficult parenteral routes of delivery which are poorly accepted by patients.

Utrogestan is intended for use in secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. When administered orally at the recommended dose, Utrogestan changes the endometrium from a proliferative to a secretory phase. Termination of the progesterone treatment results in shedding of the endometrium, i.e. menstruation.

Preclinical studies in support of the safety of Utrogestan included pharmacological and metabolism studies, acute toxicity, a 28-day study in male and female rats, and 12-week studies in female rats and female dogs. (The 12-week studies were conducted in female animals only since the therapeutic use is limited to females.) The mean particle size of the micronized progesterone used in the animal studies appeared to be ca. 5μ - possibly slightly smaller (?) than that of the present clinical form.

Studies in rats and rabbits showed the micronized form of progesterone to be more active than the normal form of progesterone but less active than the parenteral preparation.

In the prepubertal female rabbit micronized progesterone in an oral aqueous suspension was 2 fold more active in increasing uterine weight and 4 to 5 fold more active in endometrial development than crystallized progesterone. In the castrated female rat it significantly increased damaged uterus weight at doses of 100 and 200 mg/day but did not provoke a decidual response at the highest dose. Crystallized progesterone had no effect at 500 mg/day.

Concentration kinetics of oral administration of an oily suspension of micronized progesterone (125, 250, 500 mg/kg) were compared with those of s.c. administration of an oily solution of progesterone (1.25, 2.5, 5 mg/kg) in oophorectomized female rats. The correlation between the dose and total radioactivity concentrations or progesterone concentrations was better following subcutaneously administered progesterone than that following orally administered micronized progesterone. However, an oily suspension of the micronized progesterone administered orally led to meaningful plasma concentrations for at least 24 hours despite considerable metabolic breakdown. Dihydroxyprogesterone represented % of plasma progesterone after subcutaneous injection and % after oral administration. At hours, the delta 4-pregnan-20 alpha ol-3-one (delta-4) metabolite was about as abundant as progesterone following s.c. administration, but was considerably less following oral administration.

No drug related mortalities occurred in the rat studies and there were no untoward effects at doses up to 45 mg/kg. However, signs of sedation, relaxation and coma were seen at levels of 135 and 250 mg/kg and salivation at 100 mg/kg. The weight gains of the females seen in the 4-week study were not apparent in the 12-week study. The increased bilirubin levels seen at 135 mg/kg in the 12-week rat study were probably evident of some slight hepatic damage although this was not confirmed histologically. Metabolic alterations known to be induced by progesterone were reported as being present. The 325 mg/kg dose produced signs of sedation and irritation in dogs. Some alterations were seen in hematology and clinical chemistry parameters. Dogs, which appear to be sensitive to progesterone, showed cholesterol, protein electrophoresis, lipoprotein electrophoresis, electrolyte balance, BUN and BSP effects.

The 4-week rat study conducted in 1977 appeared to be more in the line of a pilot study since it was somewhat limited in that there were no hematology, clinical chemistry or urinalysis examinations and the histology consisted of examination of the liver only.

The results of these studies show that enough micronized progesterone was absorbed by oral administration to induce some of the known toxic effects of other forms of progesterone. In general the alterations found were in agreement with known effects produced by progesterone.

It would appear from the clinical studies that food may enhance blood levels of the drug (possibly a result of an alteration in the hepatic clearance of the drug due to the effect of food). In this regard the LD_{50} of the drug might actually be lower in the presence of food. Food was withheld overnight from the rats in the acute toxicity study. The time of dosing did not appear to be coordinated with food availability in the subacute rat and dog studies.

With regard to GLPs, the sponsor states in referenced IND (Item 16) that the preclinical studies (summarized in the IND) were performed in support of foreign licensing applications, and were conducted in non-U.S. laboratories. The sponsor believes that the studies were conducted in close compliance with GLP regulations and according to strict scientific method. Individual subacute preclinical studies (in the NDA) contained signed statements by the contracting laboratories to the effect that the work was performed under their supervision according to the procedures described, and that the report provides a correct and faithful or accurate record of the results obtained. The preclinical studies referred to were conducted prior to the 20 June 1979 GLP regulations compliance date.

Although the toxicity of progesterone has been extensively tested in a number of animal models, there has been no examination of its potential long-term toxicity when administered orally. We are particularly concerned about the potential for liver toxicity from chronic high-dose progesterone treatment.

As per letter to the sponsor of 24 June 1987, it will not be necessary to perform a 2-year carcinogenicity study for approval of Utrogestan for the

present indication which has previously been approved for oral medroxyprogesterone acetate. However, should the indication be expanded to include chronic use, a 2-year rat carcinogenicity study will be required.

From the standpoint of Pharmacology, no unexpected toxicity would be anticipated, and thus, we have no objection to approval of this NDA for short term use of Utrogestan in secondary amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

NOTE:

Reports containing more complete data requested to back-up the summaries of those preclinical studies contained in the original IND submission were included in the NDA and in the 6 May 87 amendment to the IND.

Sponsor needs to include section on carcinogenesis mutagenesis & impairment of fertility - in label

/S/

David H. Hertig
Pharmacologist

cc:
Original NDA 19-781; IND
HFD-345
HFD-510 JWeissinger
HFD-510 NDA 19-781; IND
HFD-510 AJordan
HFD-510 DHertig

/S/
8/11/89

DEC 2 1996

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

Also in the **Overdose** section, references to [redacted] 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.

Revisions reflected in most recent labeling dated May, 1995

/S/ 12/2/96

Krishan L. Raheja, DVM, PhD

A Jordan 12/2

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

JUN 13 1

N19781.feb96

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

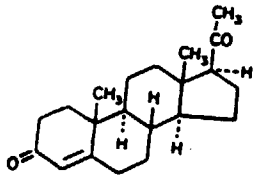
Indication: Secondary amenorrhea

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.

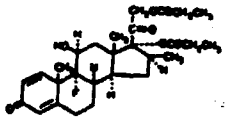
This amendment is in response to Division's non-approvable letter of August 17, 1990.

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

A Jordan 6/13

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 19-781/Drug Class: 3C

AUG - 4 1989

Applicant: La Salle Laboratories

Name of Drug: Utrogestan (progesterone, USP) Capsules

Indication: Secondary Amenorrhea

Documents Reviewed: Volume 2.1 of NDA 19-781 dated March 17, 1989, and Volume 1 of NDA 19-781 dated May 24, 1989

Medical Reviewer: This review has been discussed with the medical officer, Ridgely C. Bennett, M.D., (HFD-510).

Relevant Issues Discussed in this Review

1. Similar results in favor of Utrogestan 300 mg over placebo were obtained with regard to the initiation of withdrawal bleeding under both withdrawal interval definitions.

2. The statistical interpretation of the primary efficacy parameter results is the same whether one considers a one-sided or two-sided alternative.

3. The sponsor should assure the FDA that patient data was not discarded due to their early termination decision.

The sponsor has submitted the results of a single-center U.S. double-blind randomized study (Protocol 02) which was conducted to compare the efficacy and safety of two strengths of Utrogestan with placebo in the initiation of withdrawal bleeding in patients with secondary amenorrhea.

Reviewer's Comments on Protocol 02

For the purpose of this study, secondary amenorrhea was defined to be the failure (of a patient documented to have had prior normal menstrual cycles) to have any interval bleeding for more than 60 days. Also, withdrawal bleeding was defined to be any bleeding or blood stained discharge passed per vagina during the withdrawal interval (time from the beginning of treatment up to and including one week following the final dose).

A total of 64 patients were enrolled and randomized to receive Utrogestan 200 mg, Utrogestan 300 mg, or placebo at bedtime for 10 days.

Key Words: early termination, one-sided, secondary amenorrhea, withdrawal bleeding, withdrawal interval

The original study plan called for 75 completed patients. However, due to enrollment difficulties, the study was terminated after only 60 completions. Consequently, the sponsor should assure the FDA that patient data was not discarded due to their early termination decision.

Two Utrogestan 200 mg patients withdrew prior to commencing double-blind treatment. An additional two patients (1 Utrogestan 200 mg, 1 Utrogestan 300 mg) were excluded from the sponsor's efficacy population due to protocol violations. The sponsor's efficacy population consisted of the remaining 60 patients (19 Utrogestan 200 mg, 20 Utrogestan 300 mg, 21 placebo).

In examining the adverse reaction data supplied by the sponsor, I failed to detect a treatment effect with respect to any specific adverse reaction. The most commonly reported adverse reactions were cramps (11 Utrogestan 200 mg, 7 Utrogestan 300 mg, 6 placebo) and lethargy (4 Utrogestan 200 mg, 4 Utrogestan 300 mg, 3 placebo).

The primary measure of effectiveness was the initiation of withdrawal bleeding during the withdrawal interval as defined above.

The sponsor compared each Utrogestan treatment group with the placebo group at the one-sided .025 significance level with respect to the primary measure of efficacy in order that the experimentwise error rate remain below the conventional .05 level.

The percentage of efficacy population patients who experienced withdrawal bleeding during the withdrawal interval in each treatment group were as follows:

Utrogestan 300 mg	18/20	90.0%
Utrogestan 200 mg	10/19	52.6%
Placebo	5/21	23.8%

In utilizing a one-sided Fisher's Exact Test, the sponsor obtained a nonsignificant ($p = .06$) result with respect to the Utrogestan 200 mg - placebo comparison. However, a highly significant difference was detected between the Utrogestan 300 mg and placebo treatment groups.

The two Utrogestan patients who were excluded from the sponsor's analyses experienced withdrawal bleeding during the withdrawal interval. Corresponding analyses which includes these patients would yield similar results.

Furthermore, the utilization of two-sided tests conducted at the .025 significant level would not alter the statistical interpretation of these results due to the highly significant Utrogestan 300 mg - placebo result.

The clinical reviewer requested that the sponsor reanalyze the data under an alternate withdrawal interval definition (time from the termination of treatment up to and including one week following the final dose).

The alternate withdrawal interval definition yielded the following withdrawal bleeding results:

Utrogestan 300 mg	16/20	80.0%
Utrogestan 200 mg	7/19	36.8%
Placebo	2/21	9.5%

The Utrogestan 200 mg - placebo comparison yielded a nonsignificant (as it did with respect to the sponsor's original withdrawal interval definition) one-sided p-value of .045 based on Fisher's Exact Test conducted at the .025 significance level. In addition, a highly significant difference was once again detected between the Utrogestan 300 mg and placebo treatment groups.

Reviewer's Concluding Comments (May be Conveyed to the Sponsor)

The results of this study indicate that a significantly greater proportion of Utrogestan 300 mg patients experience withdrawal bleeding (during each of the sponsor's defined withdrawal intervals) than do placebo patients. However, statistical significance was not obtained with regard to the Utrogestan 200 mg-placebo comparisons.

This interpretation of the primary efficacy parameter data is independent of whether one considers a one-sided or a two-sided alternative.

However, the sponsor should assure the FDA that patient data was not discarded due to their early termination decision.

/S/

Daniel N. Marticello
Mathematical Statistician

This review consists of 4 pages of text.

Concur: Dr. Chi Chi 8/4/89

Dr. Dubey 8-4-89

cc:
Original NDA 19-781
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Bennett
HFD-510/Mr. Eastep
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: 1.3.2. NDA]
HFD-713/Dr. Chi
HFD-713/Mr. Marticello
Chron.
D.N.Marticello:x34594:SERB:skj:08-02-89:#2012n

JUL 7 1996

STATISTICAL REVIEW AND EVALUATION

NDA#: 19-781/Drug Class 3S

APPLICANT: Schering Corporation

NAME OF DRUG: Prometrium (progesterone) Capsules

INDICATION: Secondary Amenorrhea

DOCUMENTS REVIEWED: Volumes 2.1-2.2, 2.24-2.30 of NDA 19-781 dated February 8, 1996

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer Craig Cropp, M.D., HFD-510

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. Study C90-557 was conducted in response to the FDA's non-approvable letter dated August 17, 1990 which was issued due to the fact that Study 02 did not examine the histologic effects of micronized progesterone on the endometrium.

2. A significantly greater proportion of the Study C90-557 Prometrium 300mg and 400mg patients experienced partial or complete secretory activity than did placebo (unopposed estrogen) patients.

3. Patients randomized to Prometrium 300mg statistically outperformed their placebo counterparts with regard to the primary efficacy parameters in Studies 02 and C90-557.

4. The clinicians should comment on the significance that only the Prometrium 400mg patients statistically outperformed their placebo counterparts with regard to the incidence of complete secretory activity.

KEY WORDS: dizziness, endometrial biopsy, endometrium, estrogen priming, histologic effects, micronized progesterone, Noyes criteria, postmenopausal, premarin, premenopausal, progestational secretory activity, secondary amenorrhea, withdrawal bleeding

BACKGROUND

An NDA was submitted by La Salle Laboratories for Utrogestan (progesterone) Capsules on March 17, 1989.

This NDA included the results of a single-center U.S. double-blind randomized Study (Study 02) which was conducted to compare the efficacy and safety of two daily dosages (200mg and 300mg) of Utrogestan with placebo in the initiation of withdrawal bleeding in patients with secondary amenorrhea.

In a statistical review and evaluation dated August 4, 1989, this reviewer noted that a significantly greater proportion of patients who received Utrogestan 300mg daily for 10 days experienced withdrawal bleeding than did placebo patients. It was also noted that statistical significance was not achieved with regard to the Utrogestan 200mg - placebo comparison.

Schering Corporation assumed ownership of NDA 19-781 on July 1, 1990. Consequently, they were the recipient of a non-approvable letter dated August 17, 1990 which was issued by the FDA due to the fact that Study 02 did not examine the histologic effects of micronized progesterone on the endometrium which is the target organ.

The sponsor, based on discussions with the FDA, designed and conducted Study C90-557 in order to address the above mentioned histologic concern. This study was designed to determine whether Prometrium (formerly known as Utrogestan) could "effectively induce endometrial secretory transformation in postmenopausal women with a proliferative endometrium induced by estrogen priming".

The remainder of this review will discuss and evaluate the results of Study C90-557.

STUDY C90-557

This U.S., randomized, double-blind, multi-center (10 centers) study was conducted in estrogen-primed postmenopausal women to determine the endometrial progestational activity of Prometrium compared to placebo (unopposed estrogen).

Study 02 evaluated progestational activity by assessing the ability of micronized progesterone to induce withdrawal bleeding in premenopausal women with secondary amenorrhea.

Study C90-557 was designed to complement Study 02 by also evaluating progestational activity. However, Study C90-557 utilized a different patient population (estrogen-primed postmenopausal women) as well as a different endpoint (endometrial light microscopic histologic characterization of secretory changes based on Noyes criteria).

Subsequent to a one-to four-week estrogen priming eligibility screening phase, eligible patients entered a six-week estrogen priming phase (Cycle 1 and Days 1-15 of Cycle 2). Patients received premarin .625mg daily in the morning throughout the study. An endometrial biopsy was performed on Day 6 of Cycle 2. Patients whose biopsy indicated the existence of a proliferative endometrium were eligible to be randomized to receive double-blind treatment once daily with the evening meal for ten days (Days 16-25) of each of 3 calendar month cycles (Cycles 2-4).

Patients were randomized to receive unopposed estrogen, or 100mg, 200mg, 300mg, or 400mg of Prometrium as explained above. A second endometrial biopsy was performed on Day 26 of the fourth cycle subsequent to the last dose of double-blind medication.

A histological assessment of the presence of progestational secretory activity was performed based on this endometrial biopsy.

In order to minimize the risk of endometrial hyperplasia, patients received 10mg of Provera daily for 14 days after the conclusion of the double-blind treatment phase.

The above mentioned histological assessment was categorical (complete secretory activity, partial secretory activity, no secretory activity) as the primary efficacy parameter was the proportion of patients whose assessment was partial or complete secretory activity.

REVIEWER'S COMMENTS ON STUDY C90-557

A total of 187 postmenopausal women were enrolled. One hundred and fifty-two of these women entered the estrogen priming phase. Of these, 128 women were randomized to receive double-blind treatment. However, only 124 women (24 placebo, 26 Prometrium 100mg, 26 Prometrium 200mg, 25 Prometrium 300mg, 25 Prometrium 400mg) received at least one dose of double-blind treatment.

Thirteen women (1 placebo, 2 Prometrium 100mg, 4 Prometrium 200mg, 4 Prometrium 300mg, 2 Prometrium 400mg) failed to complete the study. The primary reason for discontinuing treatment was the occurrence of adverse experiences (1 Prometrium 200mg, 2 Prometrium 300mg, 2 Prometrium 400mg). One of the 400mg Prometrium patients discontinued due to dysmenorrhea and irritability. The remaining 4 Prometrium patients discontinued due to mild to severe dizziness.

In examining the adverse experience data submitted by the sponsor, I failed to detect a treatment effect with respect to any specific adverse experience . The most commonly reported Prometrium adverse experience was dizziness which was reported by 16 (4 Prometrium 200mg, 6 Prometrium 300mg, 6 Prometrium 400mg) Prometrium patients compared to only 1 placebo patient (p=.19).

The sponsor's efficacy population consisted of the 107 patients who completed 3 cycles of double-blind treatment and who had evaluable endometrial biopsies.

The results of the sponsor's primary efficacy parameter analyses for the 107-patient efficacy population are displayed in Table 1. In examining this table, one notes that a significantly greater proportion of Prometrium 300mg and 400mg patients experienced partial or complete secretory activity than did the corresponding placebo patients. In addition, a significantly greater proportion ($p<.001$) of Prometrium 400mg patients experienced complete secretory activity than did placebo patients.

Fifteen of the 17 (1 placebo, 4 Prometrium 100mg, 5 Prometrium 200mg, 4 Prometrium 300mg, 3 Prometrium 400mg) patients who were excluded from the sponsor's efficacy population did not have a cycle 4 biopsy performed. A Prometrium 100mg patient did not have her cycle 4 biopsy (no secretory activity) performed within 24 hours of the last double-blind treatment dose and a Prometrium 400mg (no secretory activity on cycle 4 biopsy) did not have a baseline (cycle 2) biopsy performed.

Results similar to those of the primary efficacy parameter analyses were obtained by the sponsor in an analyses in which the 17 excluded patients were assumed to have no secretory activity. A worst case analysis also yielded similar results as only 1 placebo patient was excluded from the sponsor's efficacy population.

REVIEWER'S CONCLUDING COMMENTS (may be conveyed to the sponsor)

The sponsor in their proposed labeling has indicated in the dosage and administration and indication sections that Prometrium Capsules may be given as a single daily dose of 300mg or 400mg in the treatment of secondary amenorrhea.

The results of Study 02 which was submitted on March 17, 1989 indicated that a significantly greater proportion of Prometrium 300mg patients experienced withdrawal bleeding than placebo patients.

The sponsor submitted the results of Study C90-557 in response to the FDA's non- approvable letter dated August 17, 1990 which was issued due to the fact that Study 02 did not examine the histologic effects of micronized progesterone on the endometrium.

The results of C90-557 which utilized a histologic endpoint indicated that a significantly greater proportion of Prometrium 300mg and 400mg patients experienced partial or complete secretory activity than placebo (unopposed estrogen) patients.

Consequently, the Prometrium 300mg daily dose statistically outperformed placebo in Studies 02 and C90-557 with respect to the primary efficacy parameters as defined in each of the studies.

However, it is a matter of clinical judgement, as to the clinical implications if any, of the fact that only the Prometrium 400mg dose statistically outperformed placebo in Study C90-557 with respect to the incidence of complete secretory activity.

/S/

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius 7/7/96

cc:
Archival NDA 19-781
HFD-510
HFD-510/SSobel,LRarick,CCropp,RBennett,EGalliers,CKish
HFD- 344/ALisook
HFD-715/Division File,Marticello
Chron.

This review consists of 5 pages of text and 1 tabular page

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TABLE 1

STUDY C90-557

PROGESTATIONAL SECRETORY ACTIVITY
EFFICACY POPULATION

	SECRETORY ACTIVITY			
TREATMENT GROUP	NONE	PARTIAL	COMPLETE	P-VALUE#
Placebo	23	0	0	
Prometrium 100mg	20	2	0	.47
Prometrium 200mg	16	5	0	.04
Prometrium 300mg	9	7	3	<.001*
Prometrium 400mg	8	4	10	<.00001*

\# Two-sided pairwise comparison between Prometrium treatment groups and placebo (unopposed estrogen) with regard to the proportion of patients with partial or complete activity.

* $p<.0125$ (Bonferroni Multiple Comparison Adjustment). In addition a significantly greater ($p<.001$) proportion of Prometrium 400mg patients had complete secretory activity than did placebo patients.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)