

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-756

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
CRINONE^R
PROGESTERONE VAGINAL GEL

NDA 20-756

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

BEST POSSIBLE COPY

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-756

CRINONE^R

PROGESTERONE VAGINAL GEL

VAGINAL GEL

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 **CRINONE^R**, **Columbia Research Laboratories, Inc.** has prepared an environmental assessment (attached) according to 21 CFR 25.31a and Tier 0 approach which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Progesterone is a chemically synthesized drug which is incorporated into a gel for assisted reproductive technology. The drug substance will be manufactured by
Appropriate environmental compliance certification is included.

The bulk drug product (gel) will be manufactured by

unit dose package at

from the foreign authorities were attached. The finished drug product will be used by consumers all over the United States.

The bulk gel will be packaged into

The appropriate licenses

The human metabolism and disposition of progesterone have been well characterized

Progesterone and its metabolites from consumer use would be expected to enter the aquatic environment. Progesterone is a naturally-occurring substance in the environment as a result of normal excretion by animals and humans. It is predicted that use of Crinone^R would not reasonably be expected to alter pre-existing environmental concentrations or distribution of

progesterone and its metabolites.

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 drug products will be disposed at the foreign facilities indicated above. The returned drug products will be disposed of in a solid waste management system in the US. The hospitals and clinics, empty or partially empty packages will be disposed 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 drugs may be disposed of in the sewer system.

The center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. 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.

4-25-97

Amit K. Mitra

DATE

PREPARED BY

Dr. Amit K. Mitra

Review Chemist, HFD-580

Reproductive and Urologic Drug Products

4/25/97

Dr. Moo-Jhong Rhee

DATE

DIVISION CONCURRENCE

Dr. Moo-Jhong Rhee

Chemistry Team Leader

HFD-820 assigned to HFD-580

5/1/97

Nancy B. Sager

DATE

CONCURRED

Nancy B. Sager

Team Leader

Environmental Assessment Team, HFD-357

Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet (drug substance)
EA submitted by the applicant

CC: Original NDA 20-756

HFD-580/Division file

HFD-580/A. Mitra

HFD-580/M.J.Rhee

HFD-580/D. Moore

357 HFD-004/FONSI File/NDA 20-756

357 HFD-004/Docket File

265 HFD-019/FOI Copy

NDA 20-756
CRINONE® (progesterone gel)
Section 3 - CMC

3.12 Environmental Assessment

[REDACTED]

3.12 Environmental Assessment

This environmental assessment (EA) was prepared using the November, 1995 CDER Guidance document entitled, "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements." The Tier 0 approach is being used due to the expected introduction concentration from use (EIC) being <1 ppb (refer to Section 3.12.6). Therefore, as indicated in the guidance document, an abbreviated environmental assessment has been prepared.

3.12.1 Date

This EA was prepared on April 18, 1997.

3.12.2 Applicant

The applicant for this NDA is Columbia Research Laboratories, Inc.

3.12.3 Address for Correspondence

All correspondence should be addressed to:

Columbia Research Laboratories, Inc.
100 No. Village Avenue
Rockville Center, NY 11570

3.12.4 Description of the Proposed Action

A. Requested Approval

Columbia Research Laboratories, Inc. Has filed NDA 20-756 for CRINONE® (progesterone gel), 8% strength, packaged in single-use, one piece polyethylene vaginal applicators. An abbreviated EA has been submitted pursuant to 21 CFR §25.31a(a)&(b).

B. Need for Action

CRINONE® is intended to be used for progesterone supplementation or replacement as part of an ART treatment for infertile women with documented or suspected progesterone

deficiency. This is accomplished by the extended-release nature of the formulation which, when administered vaginally (i.e., locally) in the presence of adequate estrogen, transforms a proliferative endometrium into a secretory endometrium.

C. Production Locations

The drug substance, progesterone, will be manufactured by:

Manufacturer:

The facility is located in an industrial area, which has a temperate climate. The facility is not in the vicinity of a river, lake, mountain, or forest.

The bulk progesterone gel will be manufactured by:

The facility is located in a residential area, which has a temperate climate. It is situated approximately one-half mile from a river. A copy of the site description has been provided in the Appendix (Section 3.2.1).

The bulk gel is filled into applicators and the applicators individually wrapped by:

The facility is located in an industrial area, which has a temperate, continental climate.

The facility is surrounded by hills.

D. Locations of Use

It is intended that CRINONE® be used primarily by patients in their homes. There is no expectation that use will be concentrated in a particular geographic area.

E. Disposal Sites

The method of disposal of rejected, expired or waste drug product is in keeping with the current practices of [REDACTED] Additional information on the manufacturing and control of the drug substance can be found in DMF [REDACTED] A copy of the DMF authorization letter is provided in the Appendix (refer to Section 3.12.15).

The method of disposal of rejected, expired or waste bulk drug substance is in keeping with current practices of [REDACTED] has been issued a manufacturer's license #ML/9394/1 from the Medicines Control Agency (MCA). A copy of the license is provided in the Appendix (refer to Section 3.12.15). Additional environmental information is provided as well.

The method of disposal of rejected, expired or waste finished drug product is in keeping with the current practices of [REDACTED] was granted permission for the filling of drugs, including sterile preparations, from the [REDACTED] A copy of the permit (original plus one translation) is provided in the Appendix (refer to Section 3.12.15). Please note that the permit is due to be renewed in September-October, 1996.

Although it is not anticipated that there will be much use in U.S. hospitals, pharmacies or clinics, empty or partially empty containers will be disposed of according to their procedures. In the home, empty or partially empty containers will be disposed of in the community's solid waste management system which may include landfills or incineration.

3.12.5 Identification of the Chemical Substance (Drug Substance) that is the Subject of the Proposed Action

A. Nomenclature

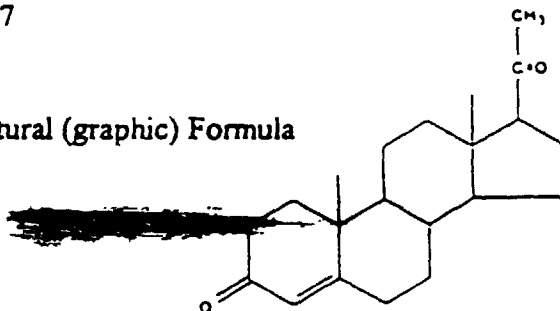
- | | | |
|------|------------------------------|------------------------|
| I. | USAN Name | Progesterone |
| II. | Brand Name | N/A |
| III. | Chemical Names | |
| | (1) Chemical Abstracts Name | Progesterone |
| | (2) Systematic Chemical Name | Pregn-4-ene-3,20-dione |

- B. Chemical Abstracts Service (CAS) Registration Number
CAS-57-83-0

- C. Molecular Formula
 $C_{21}H_{30}O_2$

- D. Molecular Weight
314.47

- E. Structural (graphic) Formula



- F. Description
White to creamy white, odorless crystalline powder

- G. Additives

The following table lists the Statement of Composition for the final formulation and the CAS Registry Numbers of each component.

CRINONE® Statement of Composition				
Component	45 mg (4%)		Function	CAS Registration Number
	mg/dose	% w/w		
✓ Progesterone (micronized)			Active Ingredient	57-83-0
✓ Glycerin			Humectant	56-81-5
			Emollient/Lubricant	8012-95-1
✓ Hydrogenated Palm Oil Glyceride			Emollient/Lubricant	*
✓ Carbomer 934			Thickening Agent	9003-01-4
✓ Sorbic Acid			Preservative	110-44-1
✓ Polycarbophil			Bioadhesive Agent	9003-97-8
✓ Sodium Hydroxide			Viscosity Adjustment by pH Control	1310-73-2
✓ Purified Water			Vehicle	7732-18-5
Notes: Commercial names are given in parentheses Each applicator delivers a dose of 1.125 g gel * = An MSDS for this product is provided in the Appendix (refer to Section 3.12.15)				

H. Impurities

Information on the ~~impurities~~ potentially involved with the manufacturing of progesterone can be found in DMF

3.12.6 Introduction of Substances into the Environment

All activities associated with the production of the drug substance and drug product are carried out outside the U.S. Certification information from the manufacturer of the drug substance, is provided in the Appendix (Section 3.12.15) Acknowledgments

from the local authorities concerning their awareness of the drug product manufacturing/packaging operations at the respective facilities can be found in the license and accompanying environmental documentation and the registration documentation in the Appendix (Section 3.12.15). Therefore, Sections 3.12.6.a-e are not applicable.

Calculation of the Expected Introduction Concentration from Use/Justification for Tier 0

The EIC calculation is based on the fifth year production and assumes that all drug product produced is evenly distributed throughout the U.S. per day, and there are no metabolism and depletion mechanisms. It should be noted that the drug substance, progesterone, is a naturally produced human hormone and is already entering the environment via the publicly owned treatment works (POTW).

$$\text{EIC-Aquatic (ppm)} = A \times B \times C \times D$$

Where

$$\begin{aligned} A &= 4000 \text{ kg/year} \\ B &= 1/\text{liter per day entering POTWs} \\ C &= \text{year}/365 \text{ days} \\ D &= 10^6 \text{ mg/kg} \end{aligned}$$

$$\text{EIC-Aquatic (ppm)} = 0.00017 \text{ ppm} = 0.17 \text{ ppb} (<1 \text{ ppb})$$

3.12.7 - 3.12.11 ~~XXXXXXXXXXXXXXXXXXXX~~

Not applicable due to the Tier 0 requirement being met.

3.12.12 List of Preparers

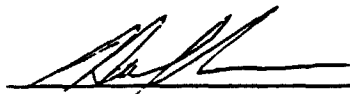
This EA was prepared by Barbara M. Finn, Director of Regulatory Operations, Quintiles Inc., RTP, NC. A copy of her CV is provided in the Appendix (refer to Section 3.12.15).

3.12.13 Certification

NDA 20-756
CRINONE® (progesterone gel)
Section 3 - CMC

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm responsible for the preparation of the EA.

The undersigned official certifies that the EA summary document (pages 1-8) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR §1506.6.



Howard Levine, Pharm D.
Vice President
Columbia Research Laboratories

3.12.14 Not applicable due to the Tier 0 requirement being met.

3.12.15 Appendices (Confidential)

SAFETY DATA SHEET

According to EC-directive 93/112/EC

PROGESTERONE**1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING**

Chemical identity	Pregn-4-ene-3,20-dione. Pregnenedione. Progesteronum.
CAS-number	57-83-0
EINECS/ELINCS	200-350-6
Formula	C ₂₁ H ₃₀ O ₂
Supplier	DIOSYNTH B.V., P.O. BOX 20, 5340 BH OSS, THE NETHERLANDS
Telephone	+31 (0)412-661333 NL
Emergency telephone	+31 (0)412-661600 NL

2. COMPOSITION/INFORMATION ON INGREDIENTS

This product is to be considered a substance in conformance with EC directives.

3. HAZARDS IDENTIFICATION

Harmful by inhalation, in contact with skin and if swallowed. Possible risks of irreversible effects. May cause sensitization by inhalation and skin contact.

4. FIRST AID MEASURES

Therapeutical category	Progestogens
BGD-code	1515
Routes of exposure	Inhalation, ingestion, mucous membrane absorption and skin absorption.
Symptoms and effects	Effects of overexposure: Harmful by inhalation, in contact with skin and if swallowed. Effects as for progestogens in general. In female: amenorrhoea, Changes in libido. Impaired glucose tolerance. . . versible ovulation in male. Effects on fertility. Effects on menstruation. Symptoms of exposure may include: headache, dizziness, gastro-intestinal complaints, nausea and vomiting, water and sodium retention. Additional remarks: May cause sensitization by inhalation and skin contact. Allergic reactions may occur.
First aid	
General	In all cases of doubt, or when symptoms persist, seek medical attention.
Inhalation	Remove from exposure, fresh air, rest, if breathing is difficult, give oxygen. Obtain medical attention immediately (show this Material Safety Data Sheet).

Unique code 0412

Date of last issue

07/11/1995

page 1 of 7

ICS 400

SAFETY DATA SHEET

According to EC-directive 93/112/EC

PROGESTERONE

Skin	Flush with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes.
Eye	Rinse immediately and as long as possible with plenty of water. Eyelids should be held away from the eyeball to ensure thorough rinsing. Seek medical advice.
Ingestion	Only when conscious, rinse mouth, give plenty of water to drink (approx. 500 ml). DO NOT induce vomiting. Seek medical advice.
Advice to physician	If swallowed (and when followed by vomiting), there is danger of aspiration.

5. FIRE-FIGHTING MEASURES

Extinguishing media	Water, fire extinguishing powder, carbon dioxide or foam.
Unsuitable extinguishing media	None.
Special exposure hazards	Emits toxic and corrosive fumes under fire conditions.
Hazardous decomposition/combustion products	None.
Protective equipment	Wear self-contained breathing apparatus, protective suit, suitable materials.
Other information	Evacuate personnel to safe area. In certain concentrations the product may form an explosive dust-air mixture.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions	Avoid inhalation of dusts. Use appropriate breathing apparatus.
Environmental precautions	Avoid dust generation. Isolate spill area.
Methods for cleaning up	Shovel up. Collect as much as possible in a clean container for (preferable) reuse or disposal. Rinse remnant with plenty of water.
Other information	-

7. HANDLING AND STORAGE

Handling	Avoid inhalation of dusts. Avoid contact with eyes, skin or clothing. Wash hands and/or face before taking a break or leaving work. Never weigh out in the storage room. Avoid exposure to women especially during pregnancy and lactation.
Fire and explosion prevention	Avoid dust generation. Take precautionary measures against static discharges.

SAFETY DATA SHEET

According to EC-directive 93/112/EC

PROGESTERONE

Storage requirements	Store in well closed containers protected from light and moisture, at 15-25 °C.
Other information	Do not eat, drink or smoke in application area. Keep working clothes separately and do not take them home.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering controls	Ensure good ventilation and local exhaust ventilation of the working area. If these measures are not sufficient, suitable respiratory protection must be worn.
Exposure limits	No exposure limit has been established.
Personal protection	
Respiratory	Use appropriate breathing apparatus.
Hand	Wear suitable gloves.
Eye	Wear safety goggles.
Skin and body	Wear suitable protective clothing: special overalls, tight fitting at neck, ankles and wrists and head covered. Change daily. Take a shower at the end of the workday.
Other information	-

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	crystalline powder
Colour	white to almost white
Odour	odourless
Boiling point/range	not applicable
Melting point/range	120-130 °C
Flash point	not applicable
Flammability	not applicable
Auto-ignition temperature	not applicable
Explosive properties	not applicable
Explosion limits	not applicable
Oxidizing properties	not applicable
Vapour pressure	not applicable
Density	not determined
Bulk density	not determined

SAFETY DATA SHEET

According to EC-directive 93/112/EC

PROGESTERONE

Solubility in water	insoluble in water
Solubility in other solvents	soluble in alcohol 1:8, chloroform 1: < 1, slightly soluble in acetone, ether, dioxane and vegetable oils
pH value	not applicable
Partition coefficient n-octanol/water	not determined
Relative vapour density air = 1	not applicable
Viscosity	not applicable
SADT	not applicable
Specific conductivity	not applicable
Other information	-

10. STABILITY AND REACTIVITY

Stability	Stable under recommended storage and handling conditions (see section 7).
Conditions to avoid	None.
Materials to avoid	None.
Hazardous decomposition products	None.
Other information	-

11. TOXICOLOGICAL INFORMATION

Acute toxicity	
Oral LD50	No data available.
Dermal LD50	No data available.
Inhalation LC50	No data available.
Irritation	
Skin	No data available.
Eye	No data available.
Respiratory	No data available.
Sensitization	No data available.
Genotoxicity	Possible risks of irreversible effects: experimental neoplastigen, carcinogen and tumorigen. Mutagenic data. Sufficient evidence of carcinogenicity in experimental animal (IARC). Progestogens: inadequate evidence of carcinogenicity in human (IARC). The group as a whole is classified as possibly carcinogenic to human, this may not apply to all individual substances within the group.



SAFETY DATA SHEET

According to EC-directive 93/112/EC

PROGESTERONE

Other toxicological information

Acute toxicity:

ori-rat LD50: > 6400 mg/kg (MEDROXYPROGESTERONE ACETATE).
lrv-mouse LD50: 100 mg/kg.

Chronic toxicity: no chronic toxicity data available.

Reproductive effects: experimental teratogen, reproductive disorder(s) in human and experimental animal.

ori-women TDLo: 100 mg/kg (20 day(s) pre-mating).

ori-rat TDLo: 25 mg/kg (female, 1 day(s) pre-mating).

ims-man TDLo: 15 mg/kg (21 day(s) pre-mating).

acu-rat TDLo: 500 10^{-3} mg/kg (female, 2 day(s) pre-mating).

RTECS No. TWO175000; N.I. Sax et al. (7Ed), 1989, p 2880; Martindale "The Extra Pharmacopoeia" (30Ed), J.E.F. Reynolds, 1993, p 1170&1194; IARC Monographs, Volume 50, 1980; IARC Monographs Suppl.7, 1987. RTECS No. TU5010000 (MEDROXYPROGESTERONE ACETATE).

12. ECOLOGICAL INFORMATION

No data available.

13. DISPOSAL CONSIDERATIONS

Product

According to local regulations: controlled incineration, controlled landfill.

Contaminated packaging

According to local regulations: controlled incineration, controlled landfill.

Other information

Non-contaminated containers can be treated like domestic garbage.
According to local regulations.

14. TRANSPORT INFORMATION

Land transport

ADR class

ADR item number

RID class

RID item number

Hazard Identification No.

Substance Identification No.

TREM-Card

UN number

Proper shipping name

Other information

No dangerous good, according to national and international transport regulations.

Sea transport

UN number

Class

Unique code 0412

Date of last issue

07/11/1995

page 5 of 7

ICS 403

SAFETY DATA SHEET

According to EC-directive 93/112/EC

PROGESTERONE

Packing group

EMS

Proper shipping name

Other information

Marine pollutant

MFAG

No dangerous good, according to national and international transport regulations.

Air transport

IATA/ICAO-DGR

Class

Proper shipping name

Other information

UN number

Packing group

No dangerous good, according to national and international transport regulations.

15. REGULATORY INFORMATION

Labelling according to

EU-number

EU directives and own criteria.

200-350-6



Symbol(s)

Xn
HARMFUL

Risk phrase(s)

R20/21/22: Harmful by inhalation, in contact with skin and if swallowed.
R40: Possible risks of irreversible effects.
R42/43: May cause sensitization by inhalation and skin contact.

Safety phrase(s)

S36/37: Wear suitable protective clothing and gloves.
S38: In case of insufficient ventilation, wear suitable respiratory equipment.
S44: If you feel unwell, seek medical advice (show the label where possible).

Other information

Micro crystalline powder, with S22: Do not breathe dust.

16. OTHER INFORMATION

This information only concerns the above mentioned product and does not need to be valid if used with other product(s) or in any process. The information is correct and complete to our best present knowledge and is given in good faith, but without warranty. It remains the user's own responsibility to make sure that the information is appropriate and complete for his special use of this product.

History

Unique code

0412

Date of last issue

07/11/1995

page 6 of 7

ICS 409



SAFETY DATA SHEET

According to EC-directive 93/112/EC

PROGESTERONE

Date of printing	23/05/1996
Revision	01
Composed by	Dept. of Safety and Environmental Affairs
Changes were made in section	1, 7, 8, 9