CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-701

ADMINISTRATIVE DOCUMENTS

NDA 20-701
Crinone™ (Progesterone gel)
Columbia Research Laboratories, Inc.

Safety Update Review

The safety update is included in Medical Officer review dated July 23, 1997.

Group Leader Memorandum

NDA:	**20-701**
Drug and indication:	**Crinone™ (4% progesterone gel) for treatment of secondary amenorrhea; Crinone™ (8% progesterone gel) for use in women who have failed to respond to treatment with Crinone™ 4%**
Dose:	**one prefilled applicator vaginally every other day up to a total of six doses**
Applicant:	**Columbia Research Laboratories, Inc.**
Submission dated:	**July 23, 1996**
Date of MO review:	**July 7, 1997**
Date of Memorandum:	**July 24, 1997**

In this application, the sponsor requests approval for Crinone™ (4 and 8% progesterone gel) for treatment of secondary amenorrhea. The primary evidence supporting the safety and efficacy of this product are the results of three small, dose-comparative trials conducted in 127 estrogen-primed women with hypothalamic amenorrhea. In these trials, withdrawal bleeding occurred in approximately 80% of women following short-term use of progesterone gel.

I concur with the recommendation of the primary reviewers that this application is approvable. However, several aspects of this drug's approvability merit comment, and are unresolved as of the date of this memorandum. Outstanding issues may be summarized as follows:

1. Study population

The primary evidence of the efficacy of progesterone gel for this indication is based on the results of studies conducted in women with hypothalamic amenorrhea, who therefore required pretreatment with estrogen before progesterone administration. The designs of these studies were previously discussed with the Division of Metabolic and Endocrine Drug Products, and it was reportedly agreed that this population was a reasonable model for secondary amenorrhea. However, the sponsor has requested an indication for a broader target population than studied (i.e., women with any etiology of secondary amenorrhea). While it reasonable to assume that this product will be efficacious in many women in the broader population, the results obtained in the clinical trial "model" population may actually overestimate the results in clinical practice. Therefore, the sponsor has been requested to commit to conducting a phase IV study of the safety and efficacy of progesterone gel in the target population in order

to provide more generalizable data in the product label.

4. Labeling

A teleconference with the sponsor will be held on July 25, 1997 to resolve the previously noted outstanding issues. If agreement on these labeling issues can not be reached, then an approvable letter should be issued pending their resolution.

Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA20-701
HFD-580/LRarick/PPrice/HJolson

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PATENT CERTIFICATION:
Paragraph I Certification

We hereby certify that in our opinion and to the best of our knowledge, the patent information for Patent No. 4,615,697 and Patent Application Serial No. 08/122,371 has not been submitted to the FDA.

Howard L. Levine, Vice President

PATENT INFORMATION

As required under 21CFR 314.53 (c), the following information is provided:

1)

(I)	U.S. Patent No. and Expiration Date:	U.S. Patent No. 4,615,697 Expiration Date - November 14, 2003
(II)	Type of Patent:	Composition and Method of Use
(III)	Name of Patent Owner:	Columbia Laboratories, Inc.

2)

(I)	U.S. Patent Application No.:	U.S. Patent Application Serial No. 08/122,371
(II)	Type of Patent:	Method of Use
(III)	Patent Owner:	Columbia Laboratories, Inc.

The undersigned declares that Patent No. 4,615,697 covers the formulation, composition and method of use of Crinone™ (progesterone vaginal gel). This product is the subject of this application for which this approval is being sought.

Howard L. Levine, Vice President

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-701 Trade (generic) names Crinone® 4%, 8% (progesterone gel)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126® for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__X__ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

_____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Diane Moore
Signature of Preparer

7/14/97
Date

cc: Orig NDA
HFD-580/Div File
NDA Action Package

COLUMBIA
RESEARCH
LABORATORIES, INC.

On behalf of Columbia Research Laboratories, Inc., I hereby certify that we did not and will not use in any capacity the services of any individual, partnership, corporation or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 20-701.

Dated: May 31, 1996

Howard L .Levine, Pharm.D.
Vice President

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Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

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Federal Register Notices

This application was not the subject of any Federal Register Notices.

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Advertising Material

No advertising material has been submitted.

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Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dr. Daniel Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Reproductive and Urologic D. P./ HFD-580
Attention: Dr. Amit K. Mitra Phone: (301) 827-4238

Date: 18-Sept-1996

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Crinone® **NDA#:** 20-701

Established name, including dosage form: Progesterone gel

Pregn-4-ene-3,20-dione
$C_{21}H_{30}O_2$, Molecular Weight: 314.5

Other trademarks by the same firm for companion products: - None

Name and address of applicant: COLUMBIA RESEARCH LABORATORIES, INC.
100 North Village Avenue, Suite 32
Rockville Centre, NY 11570

Indications for Use (may be a summary if proposed statement is lengthy): Crinone® vaginal gel is indicated for secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

Dosage Form: Vaginal gel **/Strengths:** 45 mg (4%w/w) and 90 mg (8% w/w)**/Route of Administration:** Vaginal/**Dispensed:** ℞(prescription)

Initial comments from the submitter (concerns, observations, etc.): The Tradename has been submitted with NDA 20-701

filename: 20682.tm

NOTE: *Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.*

Rev Oct. 1993