CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-756

ADMINISTRATIVE DOCUMENTS

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

NDA # 20-756 Trade (generic) names Crinone (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(c) for waiver of the requirement at 21 CFR 201.57(f) for A&MC 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.

____ b. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Duane Moore
Signature of Preparer

5-2-97
Date

cc: Orig NDA
HFD-___/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 20-756.

Dated: October 31, 1996

Howard L .Levine, Pharm.D.
Vice President

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NDA 20-756
Crinone™ (Progesterone gel)
Columbia Research Laboratories, Inc.

Division Director's Memo

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

Group Leader Memorandum

NDA:	**20-756**
Drug and indication:	**Crinone ® (8% progesterone gel) for progesterone supplementation or replacement as part of an assisted reproductive technology (ART) treatment for infertile women with progesterone deficiency.**
Dose:	**90 mg once or twice daily intravaginally (for up to 10-12 weeks if pregnancy occurs) in a prefilled applicator**
Applicant:	**Columbia Research Laboratories, Inc.**
Submission dated:	**November 13, 1996**
Date of MO review:	**April 25, 1997 (draft)**
Date of Memorandum:	**May 11, 1997**

In this application, the sponsor requests approval for Crinone ® (8% progesterone gel) for progesterone supplementation or replacement as part of an assisted reproductive technology (ART) treatment for infertile women with progesterone deficiency. The primary source of evidence supporting the safety and efficacy of this product is the results of a randomized, single-center, open-label study conducted in the United States (COL1620-007US) in 99 agonadal women who were candidates for donor egg transfer. A second randomized, open-label, multicenter study (COL1620-F01) was conducted in Europe in 283 women with tubal, idiopathic, or endometriosis-linked infertility and was submitted as supportive evidence of the safety and efficacy of progesterone gel as part of *in vitro* fertilization procedures.

I concur with the recommendation of the primary reviewers that this application is approvable. However, several aspects of this drug's development and approval merit comment:

1. Limited nature of data in support of efficacy

The primary evidence of the efficacy of progesterone gel for this indication is based on the results of one single-center, open-label study in which 54 progesterone gel-recipients received a donor egg transfer. Although a small active control group was incorporated into the study design, this active agent, IM progesterone, is not approved for this indication. However, despite this limited database, the division determined at the time of filing that this study could provide sufficient evidence of efficacy because:

a. Various unapproved formulations of progesterone are widely used in ART procedures whenever progesterone deficiency is suspected. Therefore, a placebo-controlled study was felt to be neither feasible nor ethical.

b. It was the opinion of the clinical reviewer that in the absence of effective progesterone supplementation the pregnancy rate in agonadal women would be essentially zero. Therefore, this study could be used to support the efficacy of progesterone gel in supporting pregnancy if the confidence intervals for the clinical pregnancy rate did not include zero.
c. As discussed at the industry meeting on December 20, 1993, the division agreed that a study using only a single center would be acceptable given the recognized expertise of the Jones Institute in this field.

2. Indication

The requested indication is for a broader population than the population studied in the pivotal trial (agonadal women). However, in previous discussions with the sponsor, the division recognized the inherent difficulties in trial design in women with ovarian function and agreed that the demonstration of efficacy in agonadal women would provide indirect evidence of efficacy in women with other causes of infertility. Therefore, because progesterone gel has been demonstrated to be safe and effective in agonadal women, it is reasonable to approve its use for other women who require progesterone supplementation during ART procedures.

3. Treatment IND

A treatment IND for the to-be-approved indication was allowed to proceed earlier in 1997. In order to expand the existing database on safety and efficacy with this product, the sponsor has agreed to submit a study report on the treatment IND experience, as a Phase IV commitment.

4. Labeling

At the time of this memorandum, the only outstanding substantive clinical labeling issues are the need to include: 1) explicit directions for appropriate intravaginal use; 2) recommendations regarding the appropriate duration and when once daily (as used in the IVF study) or twice daily dosing (as used in the donor egg study) is indicated; and 3) inclusion of a precautionary statement regarding the effect of progesterone on serum lipids. It is expected that these issues will be satisfactorily addressed by the time of the regulatory action.

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

cc:
NDA20-756
HFD-580/LRarick/RBennett/HJolson

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NDA 20-756
Crinone™ (Progesterone gel)
Columbia Research Laboratories, Inc.

Safety Update Review

The safety update is included in Medical Officer review dated May 2, 1997.