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APPLICATION NUMBER: NDA 20-756

PHARMACOLOGY REVIEW(S)

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NDA 20-756

Columbia Research Laboratories
Rockville, NY

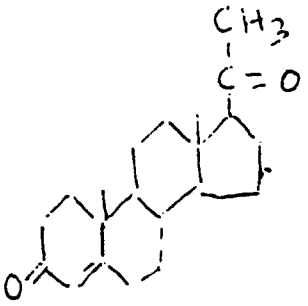
Submission dated: 11-13-1996 Received at CDER: 11-13-1996

Pharmacology review of Original NDA Submission

Drug's proprietary name: Crinone
Drug's Code name: COL-1620
IUPAC (Chemical) name: Pregn-4-ene-3,20-dione.

Pharmacologic class: Progesterone, a naturally occurring steroid that is secreted by the ovary, placenta and adrenal gland.

Molecular structure:



Molecular formula: C21 H30 O2 Molecular weight: 314.47

Dosage form: gel Strength: 8%

Composition and function of dosage form components: was described in the original IND submission

Route of administration: vaginal

Proposed indication: progesterone supplementation or replacement as part of an Assisted Reproductive technology (ART) treatment for infertile women with documented or suspected progesterone deficiency.
How supplied: 90 mg(8%) in a single use, one piece, disposable, white polyethylene vaginal applicator with a twist-off top. Each applicator contains 2.6 g and delivers 1.125 g of gel.

Dosing schedule: Crinone 90 mg is applied daily in women without

ovarian function undergoing estrogen/Crinone physiologic hormone replacement cycles designed for an Assisted Reproductive Technology (ART, donor oocyte transfer process) procedure. Crinone administration is begun on Day 14 of the cycle and continued, if a pregnancy occurred for about 10-12 weeks.

Related IND, DMF and NDA: IND
DMF and NDA 20-701 (Crinone).

Sponsor's correspondence the Division: Subsequent to submission of IND the sponsor had number of meetings with the Division to discuss and have Division's agreement on studies required for the use of Crinone in ART procedures. These discussions and agreements have been summarized as follows:

1. If Crinone was effective in initiating and maintaining pregnancy in women with no endogenous progesterone who were undergoing in vitro fertilization, it would support an indication for ART,
2. the primary efficacy variable was defined as pregnancy at 12 weeks determined by HCG levels and ultrasound,
3. proposed dose of Crinone will be 180 mg per day (90 mg b.i.d.),
4. although use of estrogen is not covered by approved labeling, it was agreed that it could be used in this study, and
5. it was decided that the primary comparison for regulatory purposes would be against historical control. However, it was thought useful to include a subgroup treated with IM progesterone.

Although Columbia Research Laboratories have already submitted NDA 20-701 for Crinone for use in patients with secondary amenorrhea or abnormal bleeding due to hormonal imbalance, it was clarified that Columbia would need to file a separate NDA for the Assisted Reproductive Technology indication. It was also agreed that the new NDA (i.e. 20-756) would consist primarily of a cross-reference to NDA 20-701, which is already under review, along with Clinical and Statistical sections of the new NDA composed of studies to support new indication.

Nonclinical pharmacology and toxicology: All studies have been reviewed under NDA 20-7~~00~~1 (Crinone for the treatment of secondary amenorrhea). Copies of the NDA 20-701 dated 8-26-1196 and that of original IND pharmacology reviews are attached.

Previous human experience: All clinical studies to support the present indication have been referred to NDA 20-701. The primary support for ART indication is from study COL1620-007US where Crinone 90 mg (b.i.d.) is compared with IM progesterone 100 mg. In this study treatments were given for 14 days during pre-donor cycle and for up to 10 weeks starting 2 days prior to embryo transfer. In an other study COL1620-F01, Crinone 90 mg is compared with Utrogestan 300 mg, 15 doses (q.d.) for 15 days following embryo transfer plus 15 additional doses (q.d.) for 15 days if pregnant on day 14.
The pregnancy rate at Day 12 was 35% for Crinone group and 30% for Utrogestan group. Clinical symptoms were significantly different in that drowsiness, decreased libido, irritability and dyspareunia were less frequent in the Crinone group.

Labeling: Proposed text of the labeling is essential similar as for NDA 20-701 except some changes which apply to present indication. The format used as well as some of the general warning and indications are those included in the currently approved labeling for progesterone or synthetic progestins. It was indicated in the labeling that the rate of malformations was similar to that reported in the literature for pregnancies following IVF procedures as in normal pregnancies.

Recommendations: Pharmacology has previously recommended approval of Crinone under NDA 20-701 for the treatment of secondary amenorrhea. Since the Crinone preparation and doses to be used for the present IVF indication are the same, Pharmacology recommends approval of Crinone for the proposed indication under NDA 20-756.

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