CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-701

PHARMACOLOGY REVIEW(S)

Kahya

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NDA 20-701

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Columbia Research Laboratories
Rockville Centre, NY

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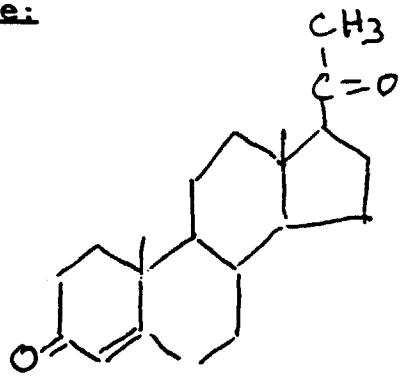
Pharmacology Review of Original NDA Submission

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 Strengths: 4% and 8%

Composition and function of dosage form components: was described in original IN

Route of administration: vaginal

Proposed indication: for the treatment of secondary amenorrhea and abnormal bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

Amenorrhea may be either primary or secondary. Primary amenorrhea is the absence of menarche. Secondary amenorrhea is defined as a failure to menstruate in women of reproductive age who have a prior history of menstruation. It could be due to deficient cyclic production of gonadotrophins or that the ovary is unresponsive. If it is due to an absence, or insufficient concentration of luteinizing hormones required for ovulation, it is called hypothalamic amenorrhea.

In secondary amenorrhea, progesterone treatment involves the conversion of estrogenized proliferative endometrium to a secretory endometrium.

Related IND:

Crinone is bioadhesive vaginal gel containing micronized progesterone in a diluted emulsion system, which is contained in single use, polyethylene vaginal applicator. The carrier vehicle is a water in oil emulsion containing the water swellable but insoluble polymer, polycarbophil. Majority of the progesterone exists as a suspension. Progesterone exists in 2 polymeric forms. Only Form 1 is said to be used in Crinone.

Each applicator contains 2.6 g and delivers 1.125 g of Crinone gel containing 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerine, mineral oil, polycarbophil, carbomer934P, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide and purified water as given in a review of the original IND

The gel-base, Replen, is stated to be a cosmetic product which is currently marketed as nonprescription vaginal moisturizer.

The polycarbophil has a slightly negative ionic charge which makes the gel bioadhesive and allows the Crinone to attach to the vaginal epithelial layer until epithelium exfoliates and is replaced by a new layer of cells, usually in about 48-72 hours. During this time progesterone is continuously released and made

available to the endometrium for absorption.

Due to Crinone's bioadhesive and sustained release properties, progesterone,s absorption is prolonged with an absorption T1/2 of approximately 25-50 hours. Its elimination T1/2 is 5-20 minutes.

Comparison of Crinone with other forms of progesterone for vaginal bioavailablity:

The bioavailability of Crinone was reported to be similar to vaginal capsule but more than 20 times higher than bioavailability of oral capsule. While the Cmax of oral progesterone was reached in 2 hour and none observed at 8 hours, levels for Crinone were 3.3 times at 2 hours and Cmax (8 times) at 8 hours. With these PK and metabolic characteristics, Crinone is prescribed to be applied every other day.

Thus there seems to be apparent preferential distribution of progesterone to the endometrium after vaginal administration expressed as "first uterine pass effect". This is based on the observation that while vaginal administration of micronized progesterone produced approximately equivalent plasma and endometrial tissue levels, after i.m administration of progesterone in oil, plasma levels were 50 times higher than endometrial tissue levels. No sig differences in endometrial thickness, ultrasound pattern, secretory development or content of estrogen and progesterone receptors were detected between 2 treatment.

Progesterone metabolites: After oral progesterone administration, aside from 5B-pregnan-3a,20a-diol glucuronide which is major metabolite in plasma and urine,(only conjugated form in circulation), plasma metabolites also include 5B-pregnan-3a-ol-20-one (5B-pregnenolone) and 5a-pregnan--3a-ol-20-one (5a-pregnenolone) which are suggested to be associated with sedation and hypnosis. The levels of these metabolites being very low after vaginal administration would not cause these side effects.

Thus the rationale of Crinone development having natural progesterone is suggested to:

1) avoid the undesired effects associated with synthetic progestins;
2) achieve endometrial progesterone concentrations sufficient to induce progestational changes without associated high plasma concentrations and
3) allow progesterone to be administered at lower doses and less frequently (every other day) due to sustained release characteristics of Crinone.

The sponsor has suggested following clinical benefits of Crinone:

1. Clinically relevant efficacy as demonstrated by an 81% and 82% incidence of menstrual bleeding in women with secondary amenorrhea,
2. Local administration of progesterone to the site of action, thereby eliminating the first-pass metabolism effects seen with oral forms of progesterone,
3. Good tolerability as demonstrated by the low incidence of adverse events, adverse event discontinuations and high compliance with study and medication administration,
4. Possible reduction in some estrogen and synthetic progestin side effect and
5. Convenience of every other day dosing.

Nonclinical pharmacology and toxicology:

The following 8 preclinical studies have been conducted in support of this NDA:

1. Acute oral toxicity in mice. Study # PH403-CL-001-92,
2. Acute oral toxicity in rats. Study # PH402-CL-001-92
3. Primary eye irritation. Study #PH421-CL-001-92.
4. Primary dermal irritation study in rabbits. Study #PH420-CL-001-92.
5. Rabbit vaginal irritation study. Study #PH427-CL-001-92.
6. Rabbit vaginal irritation study. (Repeat study) Study #PH427-CL-001.92.
7. Subacute rabbit vaginal irritation study. Study # PH427A-CL-001-91.
8. Guinea pig sensitization maximization test
   Study # PH423-CL-001-92.

All these studies were reviewed under IND

As regards toxicity of progesterone, the sponsor has stated that a review of the literature did not reveal any published studies in which progesterone was administered intravaginally. Studies of repeated dose toxicity, reproductive effects, mutagenic potential and carcinogenic potential were considered inappropriate by the sponsor for this product.

Comments: Sponsor may justify not testing reproductive effects and mutagenic potential for the present indication because of treatment's short duration, but it may not be true for some other indications where treatment is to be continued on daily basis for long periods, as in HRT or for indication such as IVF where teratogenicity would be a concern when used during the first trimester of pregnancy as indicated.

Under toxicity studies for the vehicle, COL 1003, one study is described in menopausal baboons which was not included in any of the IND submissions. Vaginal application of the vehicle was reported to have beneficial effects on secretions and moisture, pH and vaginal biopsy, and vaginal smear and mucosa rating. All these changes suggested improvement in vaginal condition.

In an in-vitro study, it was reported that polycarbophil (a polymer of polyacrylic acid) did not affect sperm motility or size of the sperm acrosomal membrane.

Clinical experience with Crinone: The sponsor has stated that a total of 16 studies involving 610 subjects treated with Crinone (45 mg, 90 mg and 180 mg of progesterone) have been completed and included in this NDA. These clinical trials consist of several PK and PD investigations of Crinone therapy for the treatment of secondary amenorrhea, in-vitro fertilization, and hormone replacement therapy. The overall number of patients with secondary amenorrhea treated with Crinone in 3 Phase III studies was 127.
It was further stated that an additional 7 clinical trials with a

planned enrollment of 239 women treated with Crinone were ongoing at the time of NDA submission. As of April, 1996, the data cut-off date for the NDA, 152 patients have been randomized to treatment with Crinone in these ongoing trials; 98 of the patients had completed these studies.

From these studies, it was concluded that the intravaginal administration of Crinone at dose of 45 mg q.o.d and 90 mg q.o.d. to women with secondary amenorrhea receiving concurrent treatment with estrogen is safe and well tolerated. At these low doses with corresponding low serum progesterone concentrations, it is associated with a reduction in the incidence of frequently reported TEAEs (treatment emergent adverse events) of the type usually associated with estrogen and progesterone use.

Labeling: The sponsor has stated that the format used for the labeling as well as some of the general warning and indications, are those included in the current approved labeling for progesterone or synthetic progestins.
The sponsor has further pointed out that they are aware that the current labeling for progestational agents includes a boxed warning concerning the use of these drugs during the first 4 months of pregnancy. However, the clinical use of natural progesterone as part of an IVF regimen has been on going for approx 15 years with no evidence of significant adverse effect. This was interpreted that clinical evidence indicates that natural progesterone can be safely used if the dose is adequately controlled and the drug is used in appropriate circumstances.

The sponsor has suggested pregnancy category A for the product. In a meeting Dr. Rarick has suggested that if the sponsor wishes to support a Pregnancy Category A statement in the labeling of COL-1620, supporting data from the literature and from the IVF studies should be provided to support the claim. Sponsor has provided some information from IVF studies although data base is very small.
Note: In a meeting held on October 27, 1995, Dr. Lisa Rarick had requested that any women in the secondary amenorrhea clinical trials who become pregnant be identified and that their CRFs should be included in the NDA.
In response the sponsor has stated that none of the patients in 3

studies for secondary amenorrhea became pregnant.
Sponsor however, has stated that of the 144 women who were treated with Crinone (90 mg q.d) during participation in an IVF program, pregnancy data outcome are available for 46 newborn in this treatment group. Two severe adverse effects were documented in 2 neonates born to women treated with Crinone. One with cleft palate and other with respiratory distress syndrome. The resulting rate of malformations was said to be similar to that reported in the literature for pregnancies following IVF procedures as in normal pregnancies.
In another meeting sponsor was asked to measure progesterone serum levels in male partners of the subjects in the intercourse kinetic study. Such data was not found in the present submission and no statement was made if such a study was conducted or not.

Subtitle on Patient Package Insert-Detailed information for the patient is missing in labeling.

Recommendations: Based on the results of preclinical studies conducted with the proposed formulation and its vehicle along with its safe and effective use in clinical trials, Pharmacology recommends approval of NDA 20-701 for the treatment of secondary amenorrhea.

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A. Jordan 8/26

Original NDA 20-701
HFD-345
HFD-580
HFD-580/A.Jordan/P.Price
HFD-580/K.Raheja, 8-23-1996, N20701.ori