

Data Sheet

CRINONE® 8 %

Progesterone 90 mg, Prolonged Release Vaginal gel with Polyethylene applicator

Presentation

CRINONE is supplied as single use, one piece, disposable, white polyethylene vaginal applicators with a twist-off top in packs of 6, 15 and 18.

Each applicator is individually wrapped and sealed in a foil over-wrap.

Each applicator contains 1.45 g of gel and delivers a constant dose of 1.125 g of CRINONE gel containing 90 mg (8 % gel) of progesterone in a base containing glycerol, paraffin-light liquid, palm glyceride-hydrogenated, carbomer 974 P, polycarbophil, sorbic acid, sodium hydroxide and purified water.

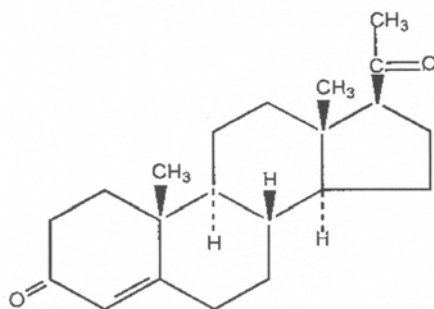
CRINONE (progesterone gel) is a bioadhesive vaginal gel, which contains micronised progesterone in a diluted emulsion system, which is contained in single use, one piece polyethylene vaginal applicators. CRINONE has the appearance of a soft, white to off-white gel.

Uses

Actions

CRINONE is administered vaginally from a pre-filled applicator and is designed to provide a prolonged release of a natural progesterone into the vagina from a polycarbophil based gel.

Natural progesterone is a hormone secreted by the corpus luteum. Progesterone is the prototype of the hormone class known as progestogens. It is chemically described as pregn-4-ene-3, 20-dione and is practically insoluble in water and soluble in most organic solvents including alcohol. Progesterone has the following chemical structure:



Chemical Formula:	C ₂₁ H ₃₀ O ₂
Molecular Weight:	314.5
Melting Range:	127-131°C
CAS:	57-83-0

The delivery system of CRINONE is based on a vaginal moisturising formulation and provides sustained topical application of progesterone into the vagina. The CRINONE delivery system is an emulsion that consists of lipophilic (lipid) and hydrophilic (aqueous) phases. The aqueous phase contains polycarbophil, a polymer that swells in the presence of water. Overall, it has a slightly negative ionic charge which produces temporary adhesion to the cell surface of the vaginal epithelium. The majority of progesterone is suspended and stored in the lipid phase while a small portion is dissolved in the aqueous phase. Absorption of progesterone occurs from the aqueous phase, which is then replenished from the lipid phase that acts as a reservoir.

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta and adrenal gland. In the presence of adequate oestrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual tissue, and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. Normal or near normal endometrial responses to exogenous oestrogen and progesterone have been noted in functionally agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory levels of gonadotropins.

Pharmacokinetics

Limited pharmacokinetic data is available for CRINONE, however studies have been conducted and the pharmacokinetic parameters from these studies can be seen in Tables 1 and 2 below.

Absorption

The bioavailability of progesterone in CRINONE was determined relative to progesterone administered intramuscularly, orally and vaginally.

In one single dose parallel group study, 18 healthy, postmenopausal women received single doses of either 90 mg progesterone vaginally in CRINONE 8% or, 100 mg progesterone orally in a capsule, or 100 mg progesterone vaginally in a capsule. The pharmacokinetic parameters are shown in Table 1.

TABLE 1			
Single dose Relative Bioavailability			
	CRINONE 8% (vaginal)	Utrogestan (oral)	Utrogestan (vaginal)
C_{max} (nmol/ ml)-plasma	32.0 ± 4.2 [‡]	61.7 ± 44.0 [‡]	21.6 ± 5.3 [‡]
T_{max} (hr)	8.3 ± 2.9 [‡]	1.8 ± 1.2 [‡]	9.0 ± 7.1 [‡]
AUC _{0-t} (nmol·hr/ ml)	584.1 ± 106.8 [‡]	309.6 ± 132.6 [‡]	666.7 ± 361.5 [‡]
$t_{1/2}$ (hr)	17.2 ± 6.3 [‡]	26.5 ± 5.7 [‡]	14.6 ± 3.9 [‡]

[‡]Mean (± SD) progesterone pharmacokinetic parameters

In a further study, comprised two crossover comparisons of progesterone pharmacokinetics in 20 healthy postmenopausal women, 10 of the subjects received a dose of 45 mg, on two different occasions; once as intravaginal gel (CRINONE 4%) and on the other as an intramuscular injection. The other 10 subjects received a dose of 90 mg by each route. The pharmacokinetic parameters are shown in Table 2.

TABLE 2 Relative Bioavailability				
	45 mg		90 mg	
	Intravaginal (CRINONE 4%)	IMI	Intravaginal (CRINONE 8%)	IMI
AUC ₀₋₉₆ (ng ml ⁻¹ /hr)	303.86± 291.38 [‡]	839.31± 115.37 [‡]	290.78± 129.90 [‡]	1378.91± 176.39 [‡]
C _{max} (mg / ml ⁻¹)	13.15± 6.49 [‡]	39.06± 13.68 [‡]	14.87± 6.32 [‡]	53.76± 14.88 [‡]
T _{max} (hr)	5.6± 1.8 [‡]	8.2± 6.4 [‡]	6.8± 3.3 [‡]	9.2± 2.7 [‡]
T _{max} (median)	5.0	5.0	6.0	8.0

[‡]Mean (± SD) progesterone pharmacokinetic parameters

These pharmacokinetic parameters show that for the 45 mg and 90 mg dose the gel is 28 % and 20 % bioavailable in comparison with the IMI route respectively.

Distribution

Progesterone is extensively bound to serum proteins (~96-99%), primarily to serum albumin and corticosteroid binding globulin.

Metabolism

The major urinary metabolite of progesterone is 5β-pregnan-3α, 20α-diol glucuronide which is present in plasma in the conjugated form only. Plasma metabolites also include 5β-pregnan-3α-ol-20-one (5β-pregnenolone) and 5α-pregnan-3α-ol-20-one (5α-pregnenolone) which may be associated with sedation and hypnosis.

Excretion

Progesterone undergoes both biliary and renal elimination. Following an injection of labelled progesterone, 50-60% of the excretion of progesterone metabolites occurs via the kidneys and approximately 10% via the bile and faeces. Overall recovery of labelled material accounts for 70% of an administered dose, with the remainder of the dose not characterised with respect to elimination. Only a small portion of unchanged progesterone is excreted in the bile.

Indications

CRINONE is used in IVF and ART, where luteal phase support is indicated.

Dosage and Administration

Reproductive failure and *in vitro* fertilisation treatment - CRINONE is given at a dose of 90 mg. CRINONE treatment is started within 4 days, preferably 2 days, after hCG (human chorionic gonadotropin) administration. One application of 90 mg (1.125 g 8% gel) should be given vaginally daily or twice daily. Most women will respond to 90 mg given daily. However, some women may need 90 mg twice daily. If pregnancy occurs treatment may continue for up to 10 to 12 weeks.

Contraindications

1. Known or suspected malignancy of the breast or genital organs.
2. Missed abortion.
3. Undiagnosed uterine bleeding.
4. Liver dysfunction or disease.
5. Known hypersensitivity to any of the components of the CRINONE formulation.
6. Known or suspected progesterone-dependent neoplasia.
7. Active thrombophlebitis or thromboembolic disorders, cerebral apoplexy, or a history of hormone associated thrombophlebitis or thromboembolic disorders.
8. Acute porphyria.

Warnings and Precautions

Warnings

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Treatment should be discontinued if the results of liver function tests become abnormal or if cholestatic jaundice appears.

Progesterone and progestins have been used to prevent miscarriage in women with a history of recurrent spontaneous pregnancy losses. No adequate evidence is available to show that they are effective for this purpose.

Precautions

1. The pre-treatment physical examination should include particular attention to the breasts and pelvic organs, and a Papanicolaou smear should be obtained.
2. As progestogens may cause some degree of fluid retention, a woman who has any condition that might be influenced by this factor (such as epilepsy, asthma, migraine, and cardiac or renal dysfunction) requires careful observation.
3. In cases of breakthrough bleeding, as with all cases of irregular vaginal bleeding, diagnostic measures may be indicated to assess whether organic disease is present.

4. Patients with a history of depression should be carefully observed and CRINONE discontinued if the depression recurs to a serious degree.
5. Progestogens may worsen the manifestations of pre-existing porphyria. Therefore the use of CRINONE in such patients is not recommended.
6. The pathologist should be advised of progestogen therapy when relevant specimens are submitted because of the influence of progestogens on the structure and pathology of organs such as the endometrium.
7. CRINONE should not be used concurrently with other local vaginal therapy (See Interactions with other Drugs).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies to determine the carcinogenic or genotoxic potential of CRINONE have been performed. Progesterone has been shown to induce and/or promote mammary, uterine, ovarian, endometrial, cervical and vaginal tumours in experimental animals. The clinical relevance of these findings is unknown.

The effect of CRINONE on fertility has not been evaluated in animals.

Use in Pregnancy - (Category A)

CRINONE has been used to successfully support embryo implantation and maintain pregnancies through its use as part of ART treatment regimens.

Use in Lactation

Do not use during lactation. Detectable amounts of progestogens have been identified in the milk of mothers receiving them. The effect of this on the nursing infant has not been determined.

Use in Children

CRINONE should not be used in children.

Effects on ability to drive or operate machinery

Drivers and users of machines are warned that risk of somnolence may occur. Special care should be taken if it is essential that patients drive or operate machinery while undergoing treatment with CRINONE.

Adverse Effects

In a study of 63 women with ovarian failure undergoing a donor oocyte transfer procedure receiving CRINONE twice daily, treatment-emergent adverse events occurring in $\geq 5\%$ of the women is shown below:

Note:

Very common: greater than or equal to 10%.
Common: greater than or equal to 1% and <10%

Body as a whole.

Very common: cramps
Common: bloating, pain

Central and Peripheral Nervous System.

Very common: headache
Common: dizziness

Gastro-Intestinal.

Common: nausea

Reproductive, female.

Very common: breast pain
Common: genital moniliasis, vaginal discharge

Skin and Appendages.

Common: genital pruritus

In the second study of 139 women using CRINONE once daily for luteal support while undergoing IVF procedure, treatment-emergent adverse events reported in $\geq 5\%$ of women is shown below:

Body as a whole.

Very common: abdominal pain, perineal pain

Central and Peripheral Nervous System.

Very common: headache

Gastro-Intestinal.

Very common: constipation, nausea,
Common: diarrhoea, vomiting

Reproductive, female.

Very common: breast enlargement
Common: dyspareunia

Musculo-skeletal.

Common: arthralgia

Psychiatric.

Very common: depression, decreased libido, nervousness, and somnolence

Urinary System.

Very Common: nocturia

In addition, intermenstrual bleeding (spotting), vaginal irritation and other mild application site reactions as well as hypersensitivity reactions usually manifesting as skin rash, have been reported post-marketing. For adverse reactions identified during post-marketing surveillance, quantification of frequency has not been attempted, but most likely uncommon to very rare.

Interactions

Interactions with other drugs:

Although no interactions with other drugs have been reported, CRINONE is not recommended for use concurrently with other vaginal preparations.

Effects on Laboratory Tests:

There is no evidence that CRINONE has any effects on laboratory tests other than endometrial histology tests.

Overdosage

There have been no reports of overdosage with CRINONE. Acute overdosage is unlikely with this product due to the concentration-dependent, rate-limited absorption of progesterone by the vaginal epithelium and the modified release characteristics of the formulation. However, in case of overdosage, discontinue CRINONE and treat the patient symptomatically.

Advise your patients to immediately contact their doctor or the Poisons Information Centre (in Australia telephone 131 126, in New Zealand telephone 0800 764 766) if they are concerned that they have given themselves too much Crinone.

Pharmaceutical Precautions

Instructions for use/handling

CRINONE is administered vaginally. Remove the applicator from the sealed wrapper. DO NOT remove the twist-off cap at this stage.

1. Grip the applicator firmly by the thick end. Shake down like a thermometer to ensure that the contents are at the thin end.
2. Twist off the tab and discard.
3. The applicator may be inserted into the vagina while the patient is in a sitting position or when lying on their back with knees bent. Gently insert the thin end of applicator well into the vagina.
4. Press the thick end of the applicator firmly to deposit gel. Remove the applicator and discard in a waste container.

CRINONE coats the vaginal mucosa to provide modified release of progesterone.

Pharmaceutical Precautions

The product must be stored below 25 °C. Shelf-life 36 months

Medicine Classification

Prescription Medicine

Package Quantities

CRINONE is supplied as single use, one piece, disposable, white polyethylene vaginal applicators with a twist-off top in packs of 6, 15 and 18.

Each applicator is individually wrapped and sealed in a foil over-wrap.

Further Information

Clinical Trials

In clinical studies of patients (n=99) with either partial or premature ovarian failure who were candidates to receive a donor oocyte transfer as an Assisted Reproductive Technology (ART) procedure were randomised to receive either CRINONE twice daily or intramuscular progesterone 100 mg daily. The study was divided into three phases. The first phase of the study consisted of a test Pilot Cycle to ensure that the administration of transdermal estradiol and progesterone would adequately prime the endometrium to receive the donor egg. The second phase was the Donor Egg Cycle during which a fertilized oocyte was implanted. CRINONE was administered beginning the evening of Day 14 of the Pilot and Donor Egg cycles. Subjects with partial ovarian function also underwent a Pre-Pilot Cycle and a Pre-Donor Egg Cycle during which time they were administered only leuprolide acetate to suppress remaining ovarian function. The Pre-Pilot Cycle, Pilot Cycle, Pre-Donor Egg Cycle, and Donor Egg Cycle each lasted approximately 34 days. The third phase of the study consisted of a 10-week treatment period to maintain a pregnancy until placental autonomy was achieved.

Sixty-one women received CRINONE as part of the Pilot Cycle to determine their endometrial response. Of the 55 evaluable endometrial biopsies in the CRINONE group performed on Day 25-27, all were histologically "in-phase" consistent with luteal phase biopsy specimens of menstruating women at comparable time intervals. Fifty-four women who received CRINONE and had an histologically "in-phase" biopsy received a donor oocyte transfer. Among these 54 CRINONE-treated women, clinical pregnancies (assessed about week 10 after transfer by clinical examination), occurred in 26 women (48%). In these 54 women, 17 women (31%) delivered a total of 25 newborns, seven women (13%) had spontaneous abortions and two women (4%) had elective abortions.

In a second study, CRINONE was used in luteal phase support of women with tubal or idiopathic infertility due to endometriosis and normal ovulatory cycles, undergoing *in vitro* fertilisation (IVF) procedures. All women received a GnRH (gonadotropin-releasing hormone) analog to suppress endogenous progesterone, human menopausal gonadotropin and human chorionic gonadotropin. In this multi-center, open labelled study 139 women (aged 22-38 years) received CRINONE once daily beginning within 24 hours of embryo transfer and continuing through 30 days post-transfer. Clinical pregnancies assessed at Day 90 post-transfer were seen in 36 (26%) of women. Thirty-two women (23%) delivered newborns and four women (3%) had spontaneous abortions.

Use of CRINONE for Pre-Menstrual Tension (PMT) and Hormone Replacement Therapy (HRT) is not supported by the information provided in this product label.

Name and Address

CRINONE is supplied in New Zealand by:

Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks, Auckland

CRINONE is supplied in Australia by:

Merck Serono Australia Pty Ltd
3-4/25 Frenchs Forest Rd
Frenchs Forest NSW 2086

Date of Preparation

02 March 2011

(CRINONE ® is a Registered Trademark)