PROPOSED PACKAGE INSERT

SCHEDULING STATUS:

S 4

PROPRIETARY NAME (and dosage form):

CRINONE® 8 % Vaginal gel

COMPOSITION:

Each applicator contains 1,45g gel and delivers a dose of 1,125g which contains

Progesterone	90 mg/dose	8,0% m/m

Preservative: Sorbic acid 0,08% m/m

List of excipients

Glycerin, Light Liquid Paraffin, Hydrogenated Palm Oil Glyceride, Carbopol 974P, Polycarbophil, Sodium Hydroxide, Purified Water.

PHARMACOLOGICAL CLASSIFICATION:

A 21.8.2 Progesterone with or without oestrogens.

PHARMACOLOGICAL ACTION:

The pharmacological action is the induction of a full secretory endometrium.

Pharmacodynamic properties

Pharmacotherapeutic group: progestogens, ATC code: G03D A04

In the presence of adequate oestrogen, progesterone transforms a proliferative endometrium into a secretory endometrium.

Pharmacokinetic properties

The progesterone vaginal gel is based on a polycarbophil delivery system, which attaches to the vaginal mucosa and provides a prolonged release of progesterone for at least three days.

Absorption

Due to the sustained release properties of CRINONE®, progesterone absorption is prolonged with an absorption half-life of approximately 25-50 hours, and an elimination half-life of 5 – 20 minutes. Therefore, the pharmacokinetics of CRINONE® are rate limited by absorption rather than elimination.

Distribution

Progesterone is extensively bound to serum proteins (approx 96 – 99%), primarily to serum albumin and corticosteriod binding globulin.

Metabolism

The major urinary metabolite of oral progesterone is 5β-pregnane-3α, 20α-diol glucuronide, which is present in plasma in the conjugated form only.

Excretion

Progesterone undergoes both biliary and renal elimination.

INDICATIONS:

Progesterone supplementation or replacement as part of an assisted reproductive technology (ART) treatment for infertile women with progesterone deficiency.

CONTRA-INDICATIONS:

CRINONE® 8% should not be used in individuals with any of the following conditions:

- Known allergy to CRINONE® (progesterone or any of the other ingredients).
- Undiagnosed uterine bleeding.
- Known or suspected malignancy of the breast or genital organs.
- Porphyria.

- Thrombophlebitis, thromboembolic disorder, cerebral apoplexy, or patients with a history of these conditions**.**
- Missed abortion.
- Liver dysfunction or disease.

WARNINGS:

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

Patients who have risk factors for thrombotic disorders should be kept under careful observation.

The product should not be used concurrently with other local intravaginal therapy. If other local intravaginal therapy is to be used concurrently, there should be at least a 6-hour period before or after CRINONE® administration.

INTERACTIONS

No interactions reported.

PREGNANCY AND LACTATION

In case of corpus luteum deficiency, CRINONE**®** can be used during the first month of pregnancy.

Do not use during lactation.

DOSAGE AND DIRECTIONS FOR USE:

Dosage

Intravaginal application.

Treatment of infertility due to inadequate luteal phase: one application (1,125 g 8 % gel) every day, starting after documented ovulation or arbitrarily on the 18th – 21st day of the cycle.
When used during *in-vitro* fertilization, daily application of CRINONE® should be continued for 30 days if there is laboratory evidence of pregnancy.

Children: not applicable.

Instructions for use/handling

CRINONE® is applied directly from the specially designed sealed applicator into the vagina.
Remove the applicator from the sealed wrapper. DO NOT remove the twist-off cap at this time.

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 while you are in a sitting position or when lying on your back with the 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.
5. CRINONE® coats the vaginal mucosa to provide long-lasting release of progesterone.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects
In clinical studies the following adverse events have been reported during CRINONE® therapy.
The adverse events reported below are classified according to the frequency of occurrence as follows:

Very common	> 1/10
Common	1/100 – 1/10
Uncommon	1/1000 – 1/100
Rare	1/10000 – 1/1000
Very rare	< 1/10000

Eye disorders

Uncommon: Xeropthalmia, conjunctivitis

Gastrointestinal disorders

Very common: Bloating, abdominal pain, constipation, nausea

Common: Diarrhoea, vomiting

Uncommon: Dry mouth, dyspepsia, eructation, flatulence, gastritis

Immune system disorders

Common: Allergy

Infections and infestations

Common: Monilliasis genital, upper respiratory tract infection, cystitis, urinary tract infection

Uncommon: Sinusitis, pharyngitis, rhinitis

General disorders and administration site conditions

Very common: Fatigue

Common: Pain, thirst

Uncommon: Asthenia, oedema, fever, influenza-like symptoms

Musculosketal and connective tissue disorders

Very common: Cramps, joint pain

Common: Arthralgia, back pain

Uncommon: Leg pain, cramps legs, skeletal pain

Metabolism and nutrition disorders

Common: Appetite increased

Uncommon: Appetite decreased, water retention

Nervous system disorders

Very common: Headache, somnolence

Common. Dizziness, syncope, migraine, tremor, forgetfulness

Psychiatric disorders

Very common:	Depression, libido decreased, nervousness, sleep disorder, emotional liability
Common:	Aggressive reactions
Uncommon:	Abnormal crying, insomnia

Renal and urinary disorders

Very common:	Nocturia
Uncommon:	Dysuria, micturation frequency

Reproductive and breast disorders

Very common:	Perineal pain, breast enlargement, breast pain, breast tenderness
Common:	Pruritis genital, dyspareuia, vaginal discharge, vaginal dryness

Respiratory system disorders

Uncommon:	Asthma, dyspnea

Skin and subcutaneous tissue disorders

Uncommon:	Sweating increased, face oedema, acne, pruritis, rash, seborrhea, skin discolouration, skin disorder, urticaria, purpura

Vascular disorders

Uncommon:	Hot flushes

All adverse events reported are included, regardless of causality. Most adverse events are mild and transient in nature, frequently resolving during continued exposure to CRINONE®.

In addition intermenstrual bleeding (spotting), vaginal irritation and other mild application site reactions have been reported post marketing.

Special precautions

1. The pretreatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

2. In cases of breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures should be undertaken.
3. Because progesterones may cause some degree of fluid retention, conditions which might be influenced by this factor (e.g. epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.
4. The pathologist should be advised of progesterone therapy when relevant specimens are taken.
5. Patients who have a history of psychic depression should be carefully observed and the medication discontinued if the depression recurs to a serious degree.
6. A decrease in glucose tolerance has been observed in a small number of patients on oestrogen-progestin combination medication. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy

Effects on ability to drive and use machines:

Drivers and users of machines are warned that risk of somnolence may occur.

Incompatibilities

No incompatibilities were found with the usual contraceptive devices.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptomatic and supportive treatment should be implemented in the case of accidental overdosage.

IDENTIFICATION:

CRINONE® gel is smooth white to off-white gel with a fatty odour. It is filled into a single use, one piece, white plastic applicator with a twist-off tab, sealed in a foil overwrap.

PRESENTATION:

The applicators are packed in cardboard boxes containing 6 or 15 applicators of CRINONE® 8 % progesterone vaginal gel.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Do not refrigerate.

Keep all medicines out of reach of children.

REGISTRATION NUMBER:

A38/21.8.2/0615

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION:

Merck (Pty) Limited

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein, Johannesburg

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