1. NAME OF THE MEDICINAL PRODUCT

Crinone 8% w/w Progesterone Vaginal Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient

	mg/dose	% w/w
Progesterone	90	8.0

Excipient with known effect: Contains Sorbic acid 0.08% w/w (0.9mg/1.125 g dose)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal Gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of infertility due to inadequate luteal phase.

For use during in-vitro fertilisation, where infertility is mainly due to tubal, idiopathic or endometriosis linked sterility associated with normal ovulatory cycles.

4.2 Posology and method of administration

Posology

Intravaginal application

Treatment of infertility due to inadequate luteal phase

One application (1.125g 8% gel) every day, starting after documented ovulation or arbitrarily on the 18^{th} – 21^{st} day of the cycle.

Use during in-vitro fertilisation

Daily application of Crinone 8% gel should be continued for 30 days if there is laboratory evidence of pregnancy.

Paediatric population
Not applicable

Older people
Not applicable

Method of Administration

Crinone is applied directly from the specially designed sealed applicator into the vagina. The applicator should be removed from the sealed wrapper. The twist-off cap should not be removed at this time.

1. The applicator should be gripped firmly by the thick end. It should be shaken down like a thermometer to ensure that the contents are at the thin end.
2. The tab should be twisted off and discarded.
3. The applicator may be inserted while patient is in a sitting position or when lying on her back with the knees bent. The thin end of applicator should be gently inserted well into the vagina.
4. The thick end of the applicator should be pressed firmly to deposit gel. The applicator should be removed and discarded in a waste container.

4.3 Contraindications

1. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
2. Undiagnosed vaginal bleeding
3. Known or suspected progesterone-sensitive malignant tumours
4. Porphyria
5. Thrombophlebitis, thromboembolic disorder, cerebral apoplexy, or patients with an history of these conditions
6. Missed abortion

4.4 Special warnings and precautions for use

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

Cautious use in severe hepatic insufficiency.

In cases of breakthrough bleeding, as in all cases of irregular vaginal bleeding, non-functional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures should be undertaken.

Crinone is not indicated in threatened abortion. Treatment should be discontinued in the event of a missed abortion.

The physician should be alert to the early manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorder, pulmonary embolism and retinal thrombosis). Should any of these symptoms occur or be suspected, the drug should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Although risk of thromboembolism has been associated with estrogens, a link with progestins remains questionable. Therefore, in women with generally recognised risk factors for thrombo-embolic events, such as personal or family history, treatment with Crinone may further increase the risk. In these women, the benefits of Crinone administration need to be weighed against the risks. It should be noted however, that pregnancy itself carries an increased risk of thrombo-embolic events.

Because progestogens may cause some degree of fluid retention, conditions that might be influenced by this factor (e.g, epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.

Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

A decrease in glucose tolerance has been observed in a small number of patients on oestrogen-progestin combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

The excipient sorbic acid may cause local skin reactions (e.g. contact dermatitis) or vaginal irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Crinone is not recommended for use concurrently with other vaginal preparations.

Although there is evidence of interaction between oral progestogens and CYP3A4 inducers, resulting in a decrease of serum progestogen levels, no significant consequences on progesterone levels is expected from concurrent administration of CRINONE® vaginal gel with CYP3A inducers.

4.6 Fertility, pregnancy and lactation

Pregnancy
In case of corpus luteum deficiency, Crinone can be used during the first month of pregnancy.

Breast-feeding
Do not use during lactation.

4.7 Effects on ability to drive and use machines

Crinone has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The adverse reactions reported below are classified according to frequency of occurrence as follows:

Very common	(³ 1/10)

Common	(³ 1/100 to < 1/10)
Uncommon	(³ 1/1,000 to < 1/100)
Rare	(³ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)

Crinone is generally well-tolerated. In clinical studies, the following adverse events have been reported during Crinone therapy. Most adverse events observed in clinical studies cannot be distinguished from the symptoms common in early pregnancy.

Common

Breast tenderness, itching or burning. Post Marketing Reports
For adverse reactions identified during post-marketing surveillance, the frequency is not known (cannot be estimated from the available data).
In addition, intermenstrual bleeding (spotting), vaginal irritation, hypersensitivity reactions usually manifesting as skin rash, and other mild application site reactions have been reported post-marketing.
Rare events of urticaria and pruritis were noted.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Not applicable.

5.1 Pharmacological properties

Pharmacotherapeutic group: Sex hormones, ATC code: G03DA04
The pharmacological particulars of the product are those of the naturally occurring progesterone with induction of a full secretory endometrium.

5.2 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.

5.3 Preclinical safety data

In rabbits, Crinone was an eye irritant categorised class IV (minimal effects clearing in less than 24 hours), but not a dermal irritant.

A moderate vaginal irritation was found in rabbits after application of 2.0ml/day of 8% gel for 5 days.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerin, Light Liquid Paraffin, Hydrogenated Palm Oil Glyceride, Carbopol 974P, Sorbic acid, Polycarbophil, Sodium hydroxide, Purified water.

6.2 Incompatibilities

No incompatibilities were found with the usual contraceptive devices.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

A single use, one piece, white polyethylene applicator with a twist-off top, designed for intravaginal application.

Each applicator contains 1.45 g of gel and delivers 1.125 gm of gel. Each one is wrapped up and sealed in a paper/aluminium/polyethylene foil overwrap.

The applicators are packed in cardboard boxes containing 6 or 15 units for Crinone 8% progesterone vaginal gel.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Merck Serono Limited
5 New Square
Bedfont Lakes Business Park
Feltham
Middlesex
TW14 8HA
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 11648/0261

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 9 June 1995
Date of latest renewal: 26 June 2004

10 DATE OF REVISION OF THE TEXT

09/12/2020