PRODUCT MONOGRAPH

CRINONE®

(Progesterone gel 8%)

Therapeutic Classification:
Progestin

Distributed by:
EMD Serono, a Division of EMD Inc., Canada
2695 North Sheridan Way, Suite 200
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CRINONE®

(Progesterone gel 8%)

Therapeutic Classification:

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ACTIONS AND CLINICAL PHARMACOLOGY

CRINONE (Progesterone gel) is a bioadhesive vaginal gel containing micronized progesterone in a diluted emulsion system. The carrier vehicle is a oil-in-water emulsion containing the water swellable, but insoluble polymer, polycarbophil. Physically, CRINONE has the appearance of a soft, white to off-white gel packed in single-use applicators designed for vaginal administration.

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen 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 oral estradiol and intramuscular progesterone have been noted in functionally agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory level of gonadotropins.

The release of progesterone from CRINONE 8% has been investigated *in vitro*.
Results indicate that approximately 65% of the progesterone is released from the gel within 24 hours, 87% is released at 48 hours, and 96% is released by 72 hours.

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

The bioavailability of progesterone in CRINONE was determined relative to progesterone administered orally and vaginally. In a parallel group study, 18 healthy, estrogenized postmenopausal women received single doses of either 90 mg progesterone vaginally in CRINONE 8%, 100 mg

progesterone orally in a capsule, or 100 mg progesterone vaginally in a capsule. After CRINONE 8% administration, the mean area under the plasma concentration curve (AUC) was 157.83 ng≅h/mL indicating a similar relative bioavailability to the vaginal capsule (247.41 ng≅h/mL) and more than 20 times higher than the bioavailability of the oral capsule (6.74 ng≅h/mL). These data suggested that when progesterone is given orally, up to 95% of the dose is eliminated by first-pass metabolism. The mean plasma concentrations following oral progesterone capsules and vaginal CRINONE administration were 1.04 and 3.49 ng/mL at 2 hours postdose (C_{max} for oral capsules), and 0 and 8.15 ng/mL at 8 hours (C_{max} for CRINONE), respectively. The variability in bioavailability was lower with CRINONE than with the capsule administered vaginally, indicating a more consistent delivery of progesterone.

The pharmacokinetics of CRINONE 90 mg administered twice daily for 12 days were studied in 10 healthy, estrogenized postmenopausal women. The average peak serum concentration achieved was 14.6 ng/mL four hours after administration. The average steady-state concentration was 11.6 ng/mL. Steady state was achieved within the first 24 hours after initialization of treatment. Upon attainment of steady-state, the disposition of progesterone administered by CRINONE suggests zero order release and absorption kinetics.

CRINONE 90 mg was applied twice daily in 50 women without ovarian function undergoing estrogen/CRINONE physiologic hormone replacement cycles designed for an Assisted Reproductive Technology (ART) procedure. Endometrial biopsies performed on Day 25-27 were histologically in-phase, consistent in morphological evaluation to natural luteal phase biopsy specimens at comparable time intervals. In this study, CRINONE was administered beginning the evening of Day 14 through Day 27 of the replacement cycle and continued if a pregnancy occurred, for about 10-12 weeks. Clinical pregnancies occurred in 48% of the women treated with CRINONE as part of their regimen.

In clinical pharmacodynamic studies, vaginal application of CRINONE containing 45 mg, 90 mg or 180 mg of progesterone every other day for a total of 6 or 7 applications resulted in mean steady state plasma progesterone concentrations of 1-4 ng/mL. CRINONE was administered in these studies from Day 15 through Day 25 of a replacement cycle. Despite the relatively low plasma progesterone concentrations, CRINONE induced a secretory transformation of the endometrium in 35 of the 36 women studied. The apparent discrepancy between the low plasma progesterone concentrations and the pronounced endometrial effects observed in these studies suggest a preferential distribution of

transvaginally administered progesterone or a First Uterine-Pass Effect [1].

INDICATIONS AND CLINICAL USE

CRINONE (Progesterone gel) 8% is indicated for luteal phase support in induced cycles such as *In Vitro* Fertilization (IVF) cycles including in oocyte donation recipient.

CONTRAINDICATIONS

CRINONE (Progesterone gel) should not be used in individuals with any of the following conditions:
Undiagnosed vaginal bleeding [2, 3],
Liver dysfunction or disease,
Known or suspected malignancy of the breast or genital organs [2, 3],
Known or suspected progesterone-dependent neoplasia,
Known sensitivity to CRINONE (progesterone or any of the other ingredients) [4],
Missed abortion [2, 3],
Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a history of these conditions [2, 3],
Acute porphyria [2, 3]

WARNINGS AND PRECAUTIONS

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. Patients who have risk factors for thrombotic disorders should be kept under careful observation.
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.
As with all prescription drugs, this medicine should be kept out of the reach of children.

General:

Crinone has moderate effect on the ability to drive and use machines. Drivers and users of machines are warned that risk of somnolence may occur [5].

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

Because progestins 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.

The pathologist should be advised of progesterone therapy when relevant specimens are submitted.

In cases of breakthrough bleeding, as in all cases of irregular bleeding per vagina, nonfunctional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures should be undertaken [2, 3].

Patients who have a history of psychic 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.

Nursing Mothers:

CRINONE should not be used during lactation. While CRINONE is administered vaginally, detectable amounts of other orally administered progesterone have been identified in the milk of mothers receiving progesterone. The possible effects of progesterone on the nursing infant have not been determined.

Pregnancy:

In case of corpus luteum deficiency, CRINONE can be used during the first trimester of pregnancy [5, 6].

CRINONE has been used to successfully support embryo implantation and maintain pregnancies through its use as part of ART treatment regimens. In fifty patients receiving donor oocyte transfer procedures, clinical pregnancies occurred in 48% of those receiving CRINONE. One woman had an elective termination of pregnancy at 19 weeks due to congenital malformations. Other deliveries resulted in normal newborns. CRINONE has been used in the luteal phase support of patients undergoing *in vitro* fertilization (IVF) procedures. In a clinical study, 139 patients received CRINONE (90 mg) once daily beginning on the day of embryo transfer and continuing through Day 30 post-transfer. The IVF success rates for pregnancies at Day 90 (26% of those transferred) and

deliveries (23% of those transferred) were similar to success rates observed in larger IVF studies. Of the 47 newborns delivered, one suffered from a teratoma associated with a cleft palate and another from respiratory distress syndrome. Forty-four newborns were normal and one was lost to follow-up. The resulting rate of malformations was similar to that reported in the literature for pregnancies following IVF procedures as in normal pregnancies [7, 8].

Drug Interaction:

Although no drug interaction with other drugs have been reported, CRINONE is not recommended for use concurrently with other local vaginal preparations. If other local intravaginal therapy is to be used concurrently, there should be at least a 6 hour period before or after CRINONE administration.

Use in Children:

Safety and effectiveness in females before menarche have not been established. As CRINONE is indicated for use in women who are post-menarcheal, pediatric use is not applicable.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 Adverse Events:

- Infections and Infestations: genital candidiasis, urinary tract infection
- Immune System Disorders: hypersensitivity
- Nervous System Disorders: headache [3], migraine, dizziness, somnolence [5]
- Gastrointestinal Disorders: abdominal pain, constipation, diarrhoea, nausea, vomiting, abdominal distension
- Psychiatric Disorders: depression, memory impairment, aggression, nervousness
- Renal and Urinary Disorders: enuresis, cystitis
- Reproductive System and Breast Disorders: libido decreased, breast tenderness [2, 3], breast pain, dyspareunia, pruritus genital, vulvovaginal dryness, vaginal discharge
- Musculoskeletal and Connective Tissue Disorders: muscle spasms, arthralgia
- General Disorders and Administration Site Conditions: fatigue, pain

- Skin and Subcutaneous Tissue Disorders: pruritis, rash, skin disorder, urticaria [9]

The adverse effects of Crinone are qualitatively identical to those described in the medical literature for natural progesterone, but their frequency appears to be lower. Most adverse events are mild and transient in nature, frequently resolving during continued exposure to Crinone.

Clinical Trial Adverse Drug Reactions

In a multiple-dose study in a total of 57 women with ovarian failure undergoing a donor oocyte transfer procedure, the most frequently reported treatment emergent adverse reactions (in decreasing order) were muscle spasms (non-specific) (16%), breast tenderness (14%), headache (12%), pain (7%), abdominal distension (7%), nausea (7%) and vaginal discharge (7%). An increase (7%) of drowsiness frequency has been reported in a study on regular IVF.

Post-Market Adverse Drug Reactions

Metrorrhagia (spotting) [10], vulvovaginal discomfort [5] and other mild application site reactions [11], as well as hypersensitivity usually manifesting as rash [11] have been reported post-marketing. For adverse reactions identified during post-marketing surveillance, quantification of frequency has not been attempted, but it is most likely uncommon to very rare.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There have been no reports of overdosage with CRINONE (Progesterone gel). Acute overdosage is unlikely with this product due to the concentration-dependent, rate-limited absorption of progesterone by the vaginal epithelium and the controlled release characteristics of the formulation. In the case of overdosage, however, discontinue CRINONE, treat the patient symptomatically, and institute supportive measures.

DOSAGE AND ADMINISTRATION

From the day of embryo transfer, one application of 1.125 g CRINONE 8% Vaginal Gel (90 mg progesterone) should be taken intravaginally once or twice daily. Most women will respond to 90 mg once daily. However, some women may need 90 mg twice daily. If pregnancy occurs treatment may continue for up to 10-12 weeks.

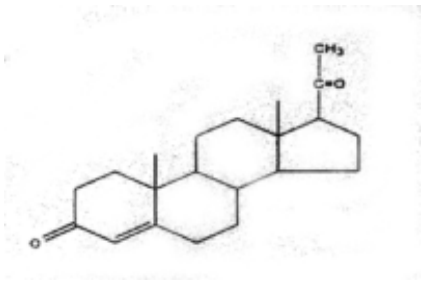
PHARMACEUTICAL INFORMATION

Drug Substance: 1,125g vaginal gel containing 90 mg progesterone

Proper Name: Progesterone

Chemical Name: Preg-4-ene-3,20-dione

Structural Formula:



Molecular Formula:	$C_{21}H_{30}O_2$
Molecular Weight:	314.47
Physical Characteristics:	White to practically white powder
Solubility:	Insoluble in water, sparingly soluble in acetone, one gram dissolves in 8mL of ethanol.
Melting range:	126ºC - 131ºC

Composition:

Active ingredient - Micronized progesterone 90 mg/1.125g.

Inactive Ingredients - carbomer 974P, glycerin, hydrogenated palm oil glyceride, light liquid paraffin, polycarbophil, sodium hydroxide, sorbic acid, purified water.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15-25º C). Avoid exposure to extreme heat or cold.

AVAILABILITY OF DOSAGE FORM

CRINONE (Progesterone gel) is available in the following strength:

90 mg (8% gel) in a single use, one piece, disposable, white polyethylene vaginal applicator with a twist-off top. Each applicator contains 1.45g of gel and delivers 1.125g of gel.

Applicators are packaged in cartons of 6 and 18 per box.

INFORMATION FOR THE CONSUMER

CRINONE

(Progesterone gel, 8%)

Please read this leaflet carefully before you start to use your medicine. Keep this leaflet, you may need to read it again. It contains a summary of the information available on your medicine. If after reading this you have any questions ask your doctor or pharmacist.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

About Your Medicine

The name of your medicine is CRINONE (Progesterone gel). Its active ingredient is progesterone. Each dose of the gel contains 90 mg / dose (8% gel) progesterone.

The gel also contains the following inactive ingredients: (alphabetically listed) Carbomer 974P, glycerine, hydrogenated palm oil glycerides, light liquid paraffin, polycarbophil, purified water, sodium hydroxide, sorbic acid.

CRINONE is available in 8% strength. It is a vaginally administered, systematically acting hormone preparation. CRINONE is a smooth white to off-white gel filled into vaginal applicators for single use.

CRINONE is available in packages of 6 or 18 applicators. CRINONE gel, containing progesterone, belongs to a group of medicines called progestins.

What Your Medicine is For

CRINONE (Progesterone gel) is used for luteal phase support in induced cycles such as *In Vitro* Fertilization (IVF) cycles including oocyte donation recipients with or without functional ovaries.

Before Using CRINONE (Progesterone gel)

Tell your doctor or pharmacist if:

you are allergic to any of the ingredients listed above;

you have abnormal vaginal bleeding;

you have porphyria (congenital or acquired disorder of the biosynthesis of the red blood stain);

you have malignant disease of the breast or genital organs, or if such a disease is suspected;

you have an acute blood clot including inflammation of superficial veins (thrombophlebitis), a vascular occlusion (thormboembolic disorder), or a cerebral apoplexy, or if you have had such disease before;
you are pregnant with a dead fetus (missed abortion);
you are breast feeding;
you have liver disease, epilepsy, heart or kidney problems, or are using any other vaginal product.

After using CRINONE (Progesterone gel)

The following side effects have been reported with CRINONE: cramps, breast pain, headache, pain, bloating, nausea,vaginal discharge, somnolence, intermenstrual bleeding, vaginal irritation and application site reactions

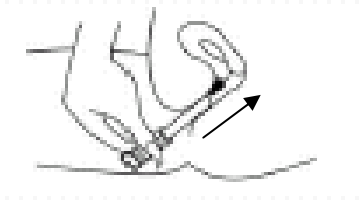
There have been occasional reports of drowsiness associated with the use of CRINONE. Therefore TAKE CARE if you intend to drive or operate machinery.

If you experience these effects and they become troublesome, please consult your doctor**.**

How to Use CRINONE (Progesterone gel)

One application of CRINONE 8% (90 mg of progesterone) every day, starting the day of the transfer. In some cases, the dose can be increased to two applications of CRINONE 8% daily. If pregnancy occurs, treatment should be continued for up to 10 to 12 weeks.

CRINONE is to be applied directly from the specially designed applicator into the vagina. CRINONE coats the vaginal mucosa to provide long-lasting release of progesterone.



Each applicator contains a slightly larger amount of gel than actually released, as the rest of the product tends to adhere to the inside of the applicator. It is therefore quite normal for a little gel to be left inside the applicator.

Each applicator contains 1.45 g vaginal gel and is designed in such way that with each administration an exactly defined amount of gel (1.125 g) is delivered. Any content of gel remaining in the applicator after use must be discarded.

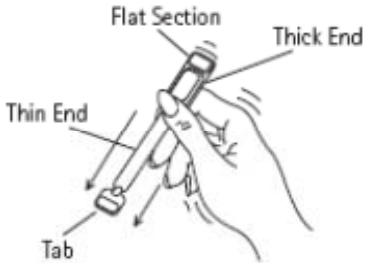
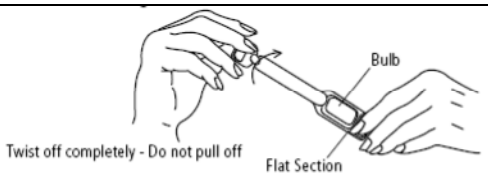
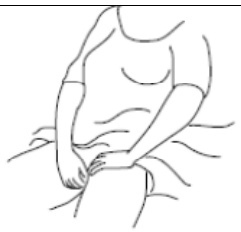
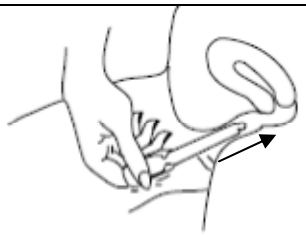
Each applicator is intended for single use only.

If you forget to use CRINONE on a normal dosage day then use it the following day and then continue as before. Do not administer double doses to make up for a forgotten single dose.

Typically the gel stays attached to the vaginal walls as the medicine absorbs. Do not be concerned if small globules appear as a discharge after several days of usage. It is common, not harmful, to have some gel residue build-up. Gel accumulation may be less likely to occur if the gel is applied in the morning because activities like walking may help spread the gel on the vaginal walls. Therefore, it is not necessary to remain lying down following administration of CRINONE. If gel accumulation becomes bothersome, talk to your doctor.

Instructions For Use

Remove the applicator from the sealed wrapper. DO NOT remove the twist-off cap at this time.

1. Grip the applicator 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 you are in a sitting position or when lying on your back with your knees bent. Gently insert the thin end as far up as you comfortably can into the vagina.	
4. Press the thick end of the applicator firmly to deposit gel. Remove the applicator and discard into a waste container.	

General Things to Remember

This medication has been prescribed only for your current medical condition. Do not use it for other medical conditions.

1. Do not allow people to use your medications and do not use medications meant for other people.
2. CRINONE should not be administered simultaneously with other intravaginal therapies. If other local intravaginal therapy is to be used simultaneously, there should be at least a 6-hour period before or after CRINONE administration. Tell any doctor treating you what medications you are taking. Always carry a medical information card stating which medications you are using. This can be very important in case you are involved in an accident.
3. Make sure that other people you live with or who look after you read this information.
4. CRINONE should not be used during lactation.
5. CRINONE must not be used in children
6. Overdosage is not anticipated because each dose is applied through an individual disposable applicator. However, if it occurs, the treatment with CRINONE 8% should be discontinued.

Storage of CRINONE (Progesterone gel)

CRINONE gel should be stored at room temperature (15-25ºC) and not exposed to extreme heat or cold. As with all medicines, the gel applicators should be kept in a safe place where children cannot reach them.

Do not use CRINONE gel after the expiry date, which is printed on the label.

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PHARMACOLOGY

There is an apparent preferential distribution of progesterone to the endometrium after vaginal administration. After seven days of vaginal administration of micronized progesterone to women with ovarian failure, the plasma and endometrial tissue levels of progesterone were approximately equivalent. However, after intramuscular administration of progesterone in oil, plasma levels were approximately 50-fold higher than the endometrial tissue levels. No significant differences in endometrial thickness, ultrasound pattern, secretory development, or content of estrogen and progesterone receptors were detected between the two treatment groups [12].

The major urinary metabolite of oral 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 5β-pregnan-3α-ol-20-one (5α-pregnenolone) which may be associated with sedation and hypnosis. After vaginal administration, the plasma concentrations of these two metabolites were substantially lower than after oral administration.

Progesterone undergoes both biliary and renal elimination. Following an injection of labeled progesterone, 50-60% of the excretion of progesterone metabolites occurs via the kidney; approximately 10% occurs via the bile and feces, the second major excretory pathway. Overall recovery of labeled material accounts for 70% of an administered dose, with the remainder of the dose not characterized with respect to elimination. Only a small portion of unchanged progesterone is excreted in the bile.

TOXICOLOGY

The nonclinical toxicology studies that have been performed include two acute toxicity studies, five local tolerance toxicity studies, and one antigenicity study. Since Progesterone, the active ingredient in CRINONE (Progesterone gel), is a naturally occurring hormone that has been extensively used in women, animal studies to assess the toxicity of progesterone have not been repeated. The toxicity studies for CRINONE focus on relevant toxicity and local tolerance.

Acute (Single-Dose) Oral Toxicity

- CRINONE was administered to CD-1 male and female mice at doses of 500, 2500, 4000, and 5000 mg/kg, and the animals were observed for up to 14 days. The estimated LD_{50} for both sexes combined was > 5000 mg/kg.
- CRINONE was administered to Sprague-Dawley male and female rats at doses of 500, 2500, and 5000 mg/kg, and the animals were observed for up to 14 days. The estimated LD_{50} for both sexes combined was > 5000 mg/kg.

Local Tolerance (Single-Dose) Toxicity

- CRINONE (0.1 mL) was instilled into the right eye of male and female New Zealand White Rabbits, and the animals were observed for up to 72 hours. CRINONE was determined to be a Class IV (minimal effects clearing in < 24 hours) eye irritant.
- CRINONE (0.5 mL) was applied to intact skin sites of male and female New Zealand White Rabbits subsequently removed after four hours of exposure. After observing the exposed intact skin sites for up to 72 hours, it was determined that CRINONE was not a dermal irritant.

Vaginal Tolerance (acute and subacute)

In two separate studies, CRINONE (2.0 mL) or 0.9% saline (2.0 mL) was administered twice daily for five consecutive days to the upper half of the vaginal tract of female New Zealand White Rabbits. The animals were sacrificed at 24 hours post-dose, and the vaginas were evaluated for histopathological changes. Severe vaginal damage (ruptured walls and abrasion of the mucosa) was noted in both treatment groups in the first study, but these effects were believed to be mechanical damage resulting from the dosing procedure. In the second study, histopathological examination showed minimal to mild vaginal irritation in animals treated with CRINONE or 0.9% saline. The extent of vaginal irritation was determined to be acceptable under the conditions of the test.

CRINONE (2.0 mL) or 0.9% saline (2.0 mL) was administered twice daily for 14 consecutive days to the upper half of the vaginal tract of female New Zealand White Rabbits. Sham controls were also included in the study. The animals were sacrificed at 48 hours after the last dose of CRINONE or saline, and the vaginas were evaluated for histopathological changes. Minimal irritation was present in five of six sham controls, four of six saline controls, and two of six CRINONE-treated rabbits. The potential of CRINONE to cause vaginal irritation was considered to be acceptable under the conditions of the test.

Antigenic Toxicity

CRINONE, 0.9% saline, or 0.1% 1-chloro-2,4-dinitrobenzene (DCNB) was administered intradermally to male and female Hartley guinea pigs. One week later, the animals were induced again by injecting the three test articles using the same injection sites utilized previously. The animals were then challenged at naive areas 14 days after the last induction period. A rechallenge evaluation with CRINONE was also conducted. CRINONE was not found to cause dermal sensitization.

The above results indicate that CRINONE is safe after acute oral ingestion, does not cause dermal or vaginal irritation and only causes transient minimal eye irritation in laboratory animals. The dose tested in the vaginal irritation studies was equivalent to approximately 80 times a human dose of 90 mg/day.

REFERENCES AND BIBLIOGRAPHY

1. Bulletti C, de Ziegler D, Flamigni C, Giacomucci E, Polli V, Bolelli G, Franceshetti F: Targeted drug delivery in gynaecology: the first uterine pass effect. Hum Reprod. 1997 May:12(5):1073-9.

2. Sweetman S. Martindale: The Complete Drug Reference. 35th ed. Pharmaceutical Press; 2007.

3. United Kingdom. Columbia Laboratories (UK) Limited. CRINONE 4% and 8% Progesterone Vaginal Gel. Clinical Expert Report. 1996 May: 1-43.

4. European Commission. A Guideline on Summary of Product Characteristics (SmPC); 2009 Sept: 1-29.

5. Pouly JL, Bassil S, Frydman R, Hedon B, Nicollet B, Prada Y, Antione JM, Zambrano R, Donnez J. Luteal support after in-vitro fertilization: Crinone 8%, a sustained release vaginal progesterone gel, versus Utrogestan, an oral micronized progesterone. Hum Reprod. 1996 Oct; 11(10):2085-9.

6. Penzias AL. Luteal phase support. Fertil Steril 2002 Feb; 77(2): 318-23.

7. Testart J, Plachot M, Mandlebau, J, Salat-Baroux J, Frydman R, Cohen J. World collaborative report on IVF-ET and GIFT: 1989 results. Hum Reprod. 1992 Mar; 7(3): 362-9.

8. Roalier A, Bachelot A, de Mouzon J, Rufat P, Logerot H. Evaluation of FIVNAT (French VF Registry) 1992. Contracept Fertil Sex. 1993 May;21(5): 354-7.

9. Columbia Laboratories, Inc. CRINONE (progesterone) gel, Human Prescription Drug Label [internet]. 2011 [updated 2009 Nov; cited 2011 Mar 31]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=13472.

10. Post-marketing data before Marketing Authorization transferred to Merck Serono (previously: Serono).

11. Fleuranceau-Morel, P. Safety Issue Work-up. CRINONE, Systemic Allergic Reactions. Geneva: Merck Serono (Switzerland); 2010 June.

12. Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmoush L, Sauer MV. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. Fertil Steril. 1994; 62: 485-90.