ENDOMETRIN® 100 mg

Vaginal tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vaginal tablet contains 100 mg progesterone.

Excipients: Silica, hydrophobic colloidal, lactose monohydrate, pregelatinised maize starch, povidone, adipic acid, sodium hydrogen carbonate, sodium laurilsulfate and magnesium stearate.

PHARMACEUTICAL FORM

Vaginal tablet
White to off-white flat and oval tablet with the inscriptions "FPI" on one side and "100" on the other side.

The vaginal tablets are supplied with one polyethylene vaginal applicator.

THERAPEUTIC INDICATIONS

ENDOMETRIN® is indicated for luteal support as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Adults

The dose of ENDOMETRIN® is 100 mg administered vaginally two or three times daily starting at oocyte retrieval and continuing for up to 10 weeks total duration (or 12 weeks of gestation).

Specific populations may derive greater benefits from BID or TID dosing regimen and the clinician can tailor treatment to the patient (see ‘Clinical efficacy and safety” section). Serum progesterone levels may be measured 7 days post fertilization and used to guide therapy.

Paediatric population

There is no relevant use of ENDOMETRIN® in the paediatric population.

Elderly

No clinical data have been collected in patients over age 65.

Use in special populations

There is no experience with use of ENDOMETRIN® in patients with impaired liver or renal function.

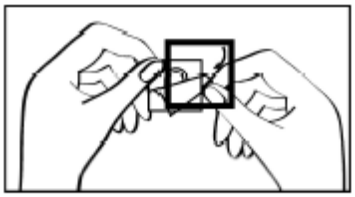
Method of Administration

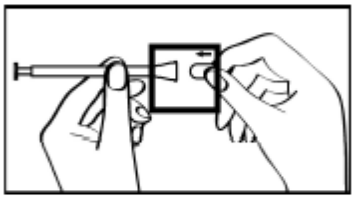
ENDOMETRIN® is to be placed directly into the vagina by the applicator provided.

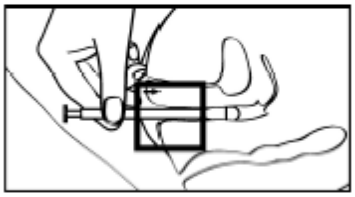
Instructions for Use

1. Unwrap the applicator.
2. Put one tablet in the space provided at the end of the applicator. The tablet should fit securely and not fall out.
3. The applicator with the tablet may be inserted into the vagina while you are standing, sitting, or when lying on your back with your knees bent. Gently insert the thin end of the applicator well into the vagina.
4. Push the plunger to release the tablet.

Remove the applicator and rinse it thoroughly in warm running water, wipe dry with a soft tissue and keep the applicator for subsequent use.







CONTRAINDICATIONS

ENDOMETRIN® should not be used in individuals with any of the following conditions:

- Hypersensitivity to the active substance or to any of the excipients listed in section QUALITATIVE AND QUANTITATIVE COMPOSITION
- Undiagnosed vaginal bleeding
- Known missed abortion or ectopic pregnancy
- Severe hepatic dysfunction or disease
- Known or suspected breast or genital tract cancer
- Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events
- Porphyria

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

ENDOMETRIN® should be discontinued if any of the following conditions are suspected: myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis, or retinal thrombosis.

Cautious use in patients with mild to moderate hepatic dysfunction.

Patients with a history of depression need to be closely observed. Consider discontinuation if symptoms worsen.

Because progesterone 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.

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

Sex steroid use may also increase the risk of retinal vascular lesions. To prevent these latter complications, caution is to be taken in users >35 years, in smokers, and in those with risk factors for atherosclerosis. Use should be terminated in case of transient ischemic events, appearance of sudden severe headaches, or vision impairments related to papillary edema or retinal hemorrhage.

Abrupt discontinuation of progesterone dosing may cause increased anxiety, moodiness, and increased sensibility to seizures.

Before starting treatment with ENDOMETRIN®, the patient and her partner should be assessed by a doctor for causes of infertility.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Drugs known to induce the hepatic cytochrome-P450-3A4 system (e.g. rifampicin, carbamazepine or St. John's wort *(Hypericum perforatum)-containing* herbal products) may increase the elimination rate and thereby decrease the bioavailability of progesterone.
In contrast ketoconazole and other inhibitors of cytochrome P450-3A4 may decrease elimination rate and thereby increase the bioavailability of progesterone.

The effect of concomitant vaginal products on the exposure of progesterone from ENDOMETRIN® has not been assessed. However, ENDOMETRIN® is not recommended for use with other vaginal products (such as antifungal products) as this may alter progesterone release and absorption from the vaginal tablet.

PREGNANCY AND LACTATION

Pregnancy:
ENDOMETRIN® vaginal tablets are only indicated during the first trimester of pregnancy for use as part of an assisted reproduction (ART) regimen.

There is yet limited and inconclusive data on the risk of congenital anomalies, including genital abnormalities in male or female infants, following intrauterine exposure during pregnancy.

In the pivotal trial, the rate of foetal anomalies following 10-week exposure to ENDOMETRIN® 100 mg three times daily was 4.5% in the ENDOMETRIN® three times daily group, a total of 7 cases of foetal anomalies (i.e. oesophageal fistula, underdeveloped right ear with hypospadias, small aorta/ valvular regurgitation/deviated septum, hand deformity, cleft palate/cleft lip, hydrocephalus and holoprosencephaly/ proboscis/ polydactylia) were seen in 404 patients. The rate of foetal anomalies observed during the clinical trial is comparable with the event rate described in the general population, although the total exposure is too low to allow conclusions to be drawn.

During the conduct of the pivotal clinical trial, the number of spontaneous abortions and ectopic pregnancies associated with the use of ENDOMETRIN® 100 mg three times daily were 5.4% and 1%, respectively.

Lactation:
Detectable amounts of progesterone have been identified in the milk of mothers. Therefore ENDOMETRIN® should not be used during lactation.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ENDOMETRIN® has minor or moderate influence on the ability to drive and use machines. Progesterone may cause drowsiness and/or dizziness; therefore caution is advised in drivers and users of machines.

UNDESIRABLE EFFECTS

The most frequently reported adverse drug reactions during treatment with ENDOMETRIN® in IVF patients during clinical trials are headache, vulvovaginal disorders and uterine spasm, reported in 1.5%, 1.5% and 1.4% subjects, respectively. The table below displays the main adverse drug reactions in women treated with ENDOMETRIN® in the clinical trial distributed by system organ classes (SOCs) and frequency.

Table 1: Main Adverse Drug Reactions in Women Treated with ENDOMETRIN® in the Clinical Trial Distributed by System Organ Classes (SOCs) and Frequency.

System Organ Class (SOC)	**Common (> 1/100 and < 1/10)**	**Uncommon (> 1/1000 and < 1/100)**	**Not known*** (cannot be estimated from the available data)**
Nervous system disorders	Headache	Dizziness, Insomnia	Fatigue
Gastrointestinal disorders	Abdominal distension Abdominal pain Nausea	Diarrhoea Constipation	Vomiting
Skin and subcutaneous tissue disorders		Urticaria Rash	Hypersensitivity reactions
Reproductive system	Uterine spasm	Vulvovaginal disorders*	

and breast disorders		Vaginal mycosis Breast disorders** Pruritus genital	
General disorders and administration site conditions		Oedema peripheral	

* Vulvovaginal disorders such as vulvovaginal discomfort, vaginal burning sensation, vaginal discharge, vulvovaginal dryness and vaginal haemorrhage, have been reported following use of ENDOMETRIN®, with cumulative reporting frequency of 1.5%.

** Breast disorders, such as breast pain, breast swelling and breast tenderness have been reported in the clinical trial as single cases, with cumulative reporting frequency of 0.4%.

*** Cases seen during post marketing experience.

OVERDOSE

High doses of progesterone may cause drowsiness.

Treatment of overdosage consists of discontinuation of ENDOMETRIN® together with institution of appropriate symptomatic and supportive care.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens; Pregnen-(4) derivatives.

ATC code: G03DA04.

Mechanism of action

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 necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

Clinical efficacy and safety

A randomized, open-label, active-controlled study evaluated the efficacy of treatment with two different daily dosing regimens of ENDOMETRIN® (100 mg twice daily and 100 mg three times daily) for luteal support as part of an Assisted Reproductive Technology (ART) treatment program for infertile women. The study included 1,211 women, of whom 1,175 women underwent embryo transfer (n=392 ENDOMETRIN® 100 mg BID, n=390 ENDOMETRIN® 100 mg TID and n=393 active comparator). Subjects ranged in age from 19 to 42 years.

The study drug was initiated on the day after oocyte retrieval and was continued for a total duration of approximately 10 weeks if the patient conceived. The patient population in this study was pre-stratified and randomised according to age (<35, 35-37, 38-40, 41-42 years). Women up to 35 years of age constituted 61% (N=737) of the trial population and the majority had FSH levels <10 IU/L (N=1047/1193, 88%). The study was powered to demonstrate non-inferiority overall for the entire trial population, not for each of the age groups.

The primary efficacy variable was ongoing pregnancy rate which was defined as the identification of foetal heart movement at approximately 6 weeks of gestation. The ongoing pregnancy rate in the study were as follows overall, and per age-strata.

Table 2: Ongoing Pregnancy Rates – ITT Population

	ENDOMETRIN® 100 mg BID	**ENDOMETRIN® 100 mg TID**	**Crinone 8% gel 90 mg QD**
ITT Population (n=1211)	(N=404)	(N=404)	(N=403)
Ongoing Pregnancy Rate, overall 95% Confidence Interval (CI) Difference between ENDOMETRIN® & Crinone [95% CI lower bound for difference]	156 (39%) [33.8, 43.6] -3.6% [-10.3]	171 (42%) [37.5, 47.3] 0.1% [-6.7]	170 (42%) [37.3, 47.2]
<35 years Ongoing Pregnancy Rate 95% Confidence Interval (CI) Difference between ENDOMETRIN® & Crinone [95% CI lower bound for difference]	(n=247) 111 (45%) [38.6, 51.4] 0.5% [-8.3]	(n=247) 117 (47%) [41.0, 53.8] 2.9% [-5.9]	(n=243) 108 (44%) [38.1, 50.9]
35-37 years	(n=89)	(n=93)	(n=98)

Ongoing Pregnancy Rate	27 (30%)	37 (40%)	41 (42%)
38-40 years	(n=55)	(n=46)	(n=53)
Ongoing Pregnancy Rate	16 (29%)	12 (26%)	16 (30%)
41-42 years	(n=13)	(n=18)	(n=9)
Ongoing Pregnancy Rate	2 (15%)	5 (28%)	5 (56%)

ENDOMETRIN® 100 mg TID met the non-inferiority criterion relative to CRINONE 8%, as ENDOMETRIN® TID was well within the 10% lower bound to demonstrate non-inferiority in ongoing pregnancy rate to CRINONE 8%. ENDOMETRIN® BID was just above the 10% lower bound in ongoing pregnancy rate.

Ongoing pregnancy and live birth rates following 10-week luteal support with ENDOMETRIN® PESSARIES are available from the Phase III clinical trial. ENDOMETRIN® 100 mg BID (N=392) was associated with an ongoing pregnancy rate of 39.8% (95% CI 34.9; 44.9) and a live birth rate of 36.0% (95% CI 31.2; 40.9) in patients who had an embryo transfer. For ENDOMETRIN® 100 mg TID (N=390), the ongoing pregnancy and live birth rates in patients with embryo transfer were 43.8% (95% CI 38.9; 48.9) and 39.5% (95% CI 34.6; 44.5), respectively.

PHARMACOKINETIC PROPERTIES

Absorption

Progesterone serum concentrations increased following the administration of the ENDOMETRIN® vaginal tablets in 12 healthy premenopausal females. On day 1 of treatment, the mean C_{max} 19.8 ± 2.9 ng/mL with a T_{max} of 17.3 ± 3.0 hours after administration of ENDOMETRIN® three times daily 8 hours apart.

On multiple dosing, steady state concentrations were attained within approximately 1 day after initiation of treatment with ENDOMETRIN®. Trough values of 10.9 ± 2.7 ng/mL were observed with an AUC_{0-24} of 436 ± 43 ng*hr/mL on Day 5.

Distribution

Progesterone is approximately 96 % to 99 % bound to serum proteins, primarily to serum albumin and corticosteroid binding globulin.

Biotransformation

Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites that are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization.

Elimination

Progesterone undergoes renal and biliary elimination.

Following injection of labelled progesterone, 50-60% of the excretion of metabolites occurs via the kidney; approximately 10% occurs via the bile and faeces. Overall recovery of the labelled material accounts for 70% of an administered dose. Only a small portion of unchanged progesterone is excreted in the bile.

PRECLINICAL SAFETY DATA

Progesterone is a well known natural reproductive steroidal hormone in humans and animals, with no known toxicological effects. Therefore no toxicity studies have been performed with this progesterone vaginal dosage form, with the exception of local tolerance and skin sensitization studies.

ENDOMETRIN® was found to be non-irritative for up to 90 days of twice daily vaginal administration in rabbits, and was also shown to be non-sensitising in Guinea pigs.

INCOMPATIBILITIES

Not applicable.

SHELF LIFE

3 years.

SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C in the original container.

NATURE AND CONTENTS OF CONTAINER

Alu/Alu blisters of 3 vaginal tablets.

The blisters are available in cartons with 21 vaginal tablets with 1 vaginal applicator.

SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

MANUFACTURED BY
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