AUSTRALIAN PRODUCT INFORMATION - ENDOMETRIN® PESSARIES (progesterone) 100 mg vaginal tablets

1 NAME OF THE MEDICINE

ENDOMETRIN PESSARIES progesterone 100 mg vaginal tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ENDOMETRIN PESSARIES (vaginal tablets) contain 100 mg progesterone (micronised) and also the following excipients: colloidal anhydrous silica, lactose monohydrate, pregelatinised maize starch, povidone, adipic acid, sodium bicarbonate, sodium lauryl sulfate, magnesium stearate.

3 PHARMACEUTICAL FORM

Pessaries.
Progesterone is a white or almost white, crystalline powder or colourless crystals which is practically insoluble in water, freely soluble in ethanol, sparingly soluble in acetone and in fatty oils.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ENDOMETRIN PESSARIES are indicated for luteal support as part of an Assisted Reproductive Technology (ART) treatment programme for infertile women.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

ENDOMETRIN administered into the vagina BID and TID dosing have both been shown to be efficacious. However specific populations may derive greater benefits from BID or TID dosing regimen and the clinician can tailor treatment to the patient. For women < 35 years of age and those patients with adequate ovarian reserve, ENDOMETRIN BID would be the appropriate dose. For patients aged 35 and older and those with diminished ovarian reserve, TID dosing would be the preferred regimen. Serum progesterone levels may be measured 7 days post fertilisation and used to guide therapy.

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

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.

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

4.3 CONTRAINDICATIONS

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

- Hypersensitivity to progesterone or to any of the excipients
- 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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ENDOMETRIN PESSARIES 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.

Use with caution 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 the case of transient ischemic events, appearance of sudden severe headaches, or vision impairments related to papillary oedema or retinal haemorrhage.

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.

Use in special populations

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

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

Paediatric Use
There is no relevant use of ENDOMETRIN in the paediatric population for the indication.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs known to induce the hepatic cytochrome-P450-3A4 system (such as rifampicin, carbamazepine and also herbal products containing St. John's wort (*Hypericum perforatum*)) may increase the elimination rate and thereby decrease the bioavailability of progesterone.

Ketoconazole and other inhibitors of cytochrome P450-3A4 may increase the bioavailability of progesterone.

The effect of concomitant vaginal products on the exposure of progesterone from ENDOMETRIN PESSARIES has not been assessed. 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
ENDOMETRIN PESSARIES are only indicated during the first trimester of pregnancy for use as part of an assisted reproduction (ART) regimen. The effect of ENDOMETRIN on fertility has not been evaluated in animals.

Use in Pregnancy (Category A)
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 TID was 4.5% in the ENDOMETRIN TID 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 TID were 5.4% and 1%, respectively.

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

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequently reported adverse drug reactions during treatment with ENDOMETRIN PESSARIES 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 (Table 1) 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

System Organ Class (SOC)	Common (≥1/100 and < 1/10)	Uncommon (≥1/1000 and < 1/100)	Unknown***
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 and breast disorders	Uterine spasm Vulvovaginal 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.
** 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.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

High doses of progesterone may cause drowsiness.

Treatment of overdose consists of discontinuation of ENDOMETRIN PESSARIES together with institution of appropriate symptomatic and supportive care.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

Clinical Trials

A multicentre, randomised, open-label Phase III study was conducted to determine the efficacy of ENDOMETRIN PESSARIES 100 mg BID and 100 mg TID administered vaginally in women undergoing IVF and to demonstrate non-inferiority of ENDOMETRIN versus Crinone 8% vaginal gel (90 mg) once daily (QD).

The primary efficacy variable was ongoing pregnancy following one treatment cycle in the efficacy population. Ongoing pregnancy was defined as identification of fetal heart movement at approximately 6 weeks of gestation. The primary analysis was performed to determine if the ongoing pregnancy rate for each dose of ENDOMETRIN was non-inferior to the comparator Crinone 8% (90 mg). To declare non-inferiority, the lower bound of the 95% confidence interval should exclude a difference greater than 10% in favour of the comparator. Thus, the trial investigated the relative efficacy of ENDOMETRIN versus the active comparator Crinone, and used -10% as non-inferiority limit based on clinical trials with gonadotrophins used for controlled ovarian stimulation. The absolute efficacy of ENDOMETRIN has not been investigated, as trials versus placebo (inactive) have not been conducted. To adjust for multiple comparisons, ENDOMETRIN 100 mg TID versus Crinone was considered the primary comparison. If the lower bound of the 95% confidence interval excluded a difference greater than 10% in favour of Crinone, then the non-inferiority of ENDOMETRIN 100 mg BID versus Crinone was assessed.

A total of 1211 patients undergoing IVF were randomised to receive either ENDOMETRIN 100 mg BID (n=404), ENDOMETRIN 100 mg TID (n=404) or Crinone 8% gel (90 mg) QD (n=403). 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 also 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 ongoing pregnancy rates 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 Ongoing Pregnancy Rate	(n=89) 27 (30%)	(n=93) 37 (40%)	(n=98) 41 (42%)
38-40 years Ongoing Pregnancy Rate	(n=55) 16 (29%)	(n=46) 12 (26%)	(n=53) 16 (30%)
41-42 years Ongoing Pregnancy Rate	(n=13) 2 (15%)	(n=18) 5 (28%)	(n=9) 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Progesterone serum concentrations increased following the administration of the ENDOMETRIN vaginal tablets in 12 healthy premenopausal females. On single dosing, the mean C_{max} of endogenous and exogenous progesterone was 17.0 ng/mL in the ENDOMETRIN twice daily (BID) group and 19.8 ng/mL in the ENDOMETRIN three times daily (TID) group.

On multiple dosing, steady state concentrations were attained within approximately 1 day after initiation of treatment with ENDOMETRIN. Both ENDOMETRIN regimens provided average serum concentrations of progesterone exceeding 10 ng/mL on Day 5. The pharmacokinetic results are summarised in Table 3.

Distribution

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

Metabolism

Progesterone is metabolised 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 metabolised in the gut via reduction, dehydroxylation, and epimerization.

Excretion
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.

Table 3: Mean (±Standard Deviation) Serum Progesterone Pharmacokinetic Parameters

Pharmacokinetic Parameter (unit)	ENDOMETRIN 100 mg BID (N=6)	ENDOMETRIN 100 mg TID (N=6)
Single Dosing		
C_{max} (ng/mL)	17.0 ± 6.5	19.8 ± 7.2
T_{max} (hr)	24.0 ± 0.0	17.3 ± 7.4
AUC_{0-24} (ng•hr/mL)	217 ± 113	284 ± 143
Day 5 of Multiple Dosing		
C_{max} (ng/mL)	18.5 ± 5.5	24.1 ± 5.6
T_{max} (hr)	18.0 ± 9.4	18.0 ± 9.4
C_{min} (ng/mL)	8.9 ± 4.5	10.9 ± 6.7
C_{avg} (ng/ml)	14.0 ± 4.8	15.9 ± 4.3
AUC_{0-24} (ng•hr/mL)	327 ± 127	436 ± 106

C_{max} Maximum progesterone serum concentration.
T_{max} Time to maximum progesterone serum concentration.
C_{avg} Average progesterone serum concentration.
AUC_{0-24} Area under the drug concentration versus time curve from 0-24 hours post dose.
C_{min} Minimum progesterone serum concentration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Progesterone did not induce dominant lethal mutations in mice or chromosomal aberrations in the bone marrow of rats in vivo. It did not induce chromosomal aberrations or sister chromatid exchanges in cultured human cells nor chromosomal aberrations or DNA strand breaks in rodent cells. Weak clastogenic activity was found for progesterone in the rat hepatocyte micronucleus test after treatment with a high oral dose (100 mg/kg). Studies on transformation of rodent cells *in vitro* were inconclusive. Variable results were obtained in the mouse lymphoma tk assay. Progesterone was not mutagenic to bacteria.

Carcinogenicity
Progesterone has been shown to induce/promote the formation of ovarian, uterine, mammary, and genital tract tumours in animals. The clinical relevance of these findings is unknown. Literature data provides no indication of potential carcinogenicity in humans. The exposure to women is relatively short and use of progesterone as part of an assisted reproduction regimen (ART) is regarded as replacement therapy.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Refer to Section 2 – **QUALITATIVE AND QUANTITATIVE COMPOSITION**

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

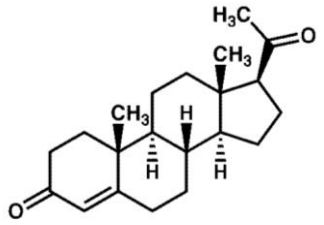
ENDOMETRIN PESSARIES containing 100 mg progesterone; white to off-white, convex and oblong tablets with the inscriptions “FPI” on one side and “100” on the other side. Nominal size approximately 22 mm x 13 mm. Supplied in alu/alu blisters packaged in an outer carton. Each carton contains 21 vaginal tablets with 1 vaginal applicator.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

The structural formula of progesterone is:



The chemical name for progesterone is pregn-4-ene-3, 20-dione.
It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5.

CAS Number
57-83-0.

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8 SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

Toll Free: 1800 337 746

9 DATE OF FIRST APPROVAL

19 September 2012

10 DATE OF REVISION

11 September 2019

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/ or http://www.ferring.com.au/

Summary table of changes

Section Changed	Summary of new information
ALL	Updated PI format to comply with the new TGA's *Form for providing Product Information,* March 2018.
2	Editorial changes to align with AAN terminology
4.4	Addition of text under "Effects on Laboratory Tests"
6.2	Addition of text under "Incompatibilities"
6.3	Addition of standard text under "Shelf Life" as per TGA's *Form for providing Product Information,* March 2018.