Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Progesterone 400 mg pessaries

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pessary contains 400 mg progesterone

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pessary

Off-white, approximately 10mm x 30mm, torpedo shaped pessary.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Progesterone is indicated for luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women.

4.2 Posology and method of administration

Posology

Adults
One 400 mg pessary administered vaginally twice a day starting at oocyte retrieval. If pregnancy has been confirmed, the administration of Progesterone should be continued for 38 days from the start of therapy.

Paediatric population
There is no relevant use of Progesterone 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 Progesterone in patients with impaired liver or renal function.

Method of administration

For vaginal insertion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Undiagnosed vaginal bleeding.
Known or suspected progesterone sensitive malignant tumours.
Porphyria.
Known missed abortion or ectopic pregnancy.
Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
Severe hepatic dysfunction or disease.

4.4 Special warnings and precautions for use

Progesterone 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.

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

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

Progesterone is metabolised in the liver and should be used with caution in patients with hepatic dysfunction.

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

4.5 Interaction with other medicinal products and other forms of interactions

Drugs known to induce the hepatic cytochrome-P450-3A4 system (e.g. rifampicin, carbamazepine or phenytoin) may increase the elimination rate and thereby decrease the bioavailability of progesterone.

The effect of concomitant vaginal products on the exposure of progesterone from Progesterone has not been assessed and is therefore not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
Progesterone is only indicated during the first trimester of pregnancy for use as part of an assisted reproduction (ART) treatment (see section 4.1 for full details). There is limited and inconclusive data on the risk of congenital anomalies, including genital abnormalities in male or female infants, following intrauterine exposure during pregnancy. The rates of congenital anomalies, spontaneous abortion and ectopic pregnancies observed during the clinical trial were comparable with the event rate described in the general population although the total exposure is too low to allow conclusions to be drawn.

Breastfeeding
Detectable amounts of progesterone have been identified in the milk of mothers. Therefore Progesterone should not be used during lactation.

4.7 Effects on ability to drive and use machines

Progesterone may cause dizziness; therefore caution is advised in drivers and users of machines.

4.8 Undesirable effects

Adverse reactions in patients undergoing luteal support as a part of ART treatment is presented in the table below:

SYSTEM ORGAN CLASS	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**
Psychiatric disorders		Mood altered
Nervous system disorder	Somnolence	Headache,

		dizziness, dysgeusia
Vascular disorders	Hot flush	Haemorrhage
Gastrointestinal disorders	Abdominal distension, abdominal pain, constipation	Diarrhoea, vomiting, flatulence, gastric dilatation
Skin and subcutaneous tissue disorders		Hypersensitivity reactions (e.g. rash, pruritus), night sweats
Musculoskeletal and connective tissue disorders		Arthralgia
Renal and urinary disorders		Pollakiuria, incontinence
Reproductive system and breast disorders	Breast pain	Vaginal haemorrhage, pelvic pain, metrorrhagia, ovarian enlargement, vulvovaginal pruritus
General disorders and administration site conditions	Fatigue	Feeling cold, feeling of body temperature change, application site pruritus, discomfort
Investigations		Weight increased

As with other vaginal preparations, some leakage of the pessary base may occur.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

4.9 Overdose

There is a wide margin of safety with progesterone pessaries, but overdosage may produce euphoria or dysmenorrhoea.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens; Pregnen-(4) derivatives. ATC code: G03DA04.

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
In a Phase III clinical trial in pre-menopausal women subjected to ART and IVF the pregnancy rates after vaginally applied Progesterone pessary (400 mg twice daily) was found to be 38.3% (FAS) and 38.1% (PP) after 38 days of luteal phase support. The clinical pregnancy rate was 34.5% after 70 days of luteal phase support.

5.2 Pharmacokinetic properties

Absorption
Vaginal administration of Progesterone400 mg every 12 h in healthy women has been shown effective in rapidly achieving and maintaining serum progesterone concentrations at physiological levels appropriate to the midluteal phase of the ovarian cycle and early pregnancy. The mean C_{max} after 10 days of multiple dosing was 18.4 [ng/mL] and C_{trough} was 10.5 [ng/mL].

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.

5.3 Preclinical safety data

Progesterone is a well-known natural reproductive steroidal hormone in humans and animals, with no known toxicological effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PE strip packs

12, 15, 30, 45 pessaries
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc
Gyömroi út 19-21
H-1103, Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER

PA1330/027/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st March 2017
Date of last renewal: 06th January 2022

10 DATE OF REVISION OF THE TEXT

October 2021