Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Microgest 200 mg Soft Gelatin Capsule

2. Qualitative and quantitative composition
The Progesterone 200 mg Soft Gelatin Capsule are constituted by the active ingredient of Progesterone BP (Micronized).

Each Progesterone 200 mg Soft Gelatin Capsule contains 200 mg Progesterone BP (Micronized)

Excipient(s) with known effect: soyabean lecithin.
For the full list of excipients, see Section 6.1.

3. Pharmaceutical form
Oval-shaped, off-white to yellowish colored soft gelatin capsule. Approximately 14.6 mm long x 9.5 mm wide

4. Clinical particulars

4.1 Therapeutic indications
Progesterone 200 mg Soft Gelatin Capsule is indicated in women for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.
Gynaecological:
Disorders related to progesterone insufficiency, In particular:
- premenstrual syndrome,
- menstrual disorders due to poor ovulation or anovulation,
- benign breast disease,
- premenopause.
- Treatment of the menopause (as an adjuvant to oestrogen therapy). - Sterility due to luteal phase deficiency.
Obstetric:
- Threat of miscarriage or prevention of recurrent miscarriages due to proven luteal phase deficiency.
- Threat of premature delivery.

4.2 Posology and method of administration
Posology
On average, the dosage is 200 to 300 mg progesterone per day, divided into one or two doses, i.e. 200 mg in the evening at bedtime plus 100 mg in the morning, if needed.
- For luteal phase deficiency (premenstrual syndrome, menstrual irregularities, premenopause, benign breast disease): the treatment is used for 10 days per cycle, usually from days 17 to 26 inclusive.
- In the treatment of menopause: as oestrogen therapy alone is not recommended, progesterone is added during the last two weeks of each treatment schedule, followed by a one-week suspension of all replacement therapy, during which withdrawal bleeding may be observed.

- For threatened premature delivery: 400 mg of progesterone every 6 to 8 hours, depending on the clinical results obtained during the acute phase, followed by a maintenance dosage (e.g. 3 x 200 mg per day) up until week 36 of pregnancy.

Method of Administration:
Oral or Vaginal

For Vaginal, each capsule of Progesterone 200 mg soft gelatin Capsules must be inserted deep into the vagina.
For Oral, Progesterone should not be taken with food, and should be taken at bedtime.
Concomitant food ingestion increases the bioavailability of micronized progesterone.

For dosage, national and local treatment guidelines should be taken into account.

4.3 Contraindications

When used in conjunction with oestrogens. Progesterone should not be used in patients with any of the following conditions:

- Known hypersensitivity to the active substances, soybean lecithin, peanut or to any of the excipients listed in section 6.1
- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (e.g. genital tract carcinoma)
- Undiagnosed genital bleeding
- Previous or current thromboembolism disorders (e.g. deep venous thrombosis, pulmonary embolism) or thrombophlebitis
- Known thrombophilic disorders
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria
- Cerebral haemorrhage
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

Progesterone 200 mg soft gelatin Capsules should only be used during the first three months of pregnancy and must only be administrated by vaginal route. The use of micronised progesterone during the second and third trimester of pregnancy may lead to the development of gravidic cholestasis or hepatocellular liver disease.
Progesterone 200 mg soft gelatin Capsules are not suitable in confirmed pregnancy (see section 4.6), in the treatment of premature labour, or as a contraceptive.
Treatment should be discontinued upon diagnosis of a missed abortion.

Precautions

Progesterone 200 mg soft gelatin Capsules contains soya lecithin and may cause hypersensitivity reactions (urticarial and anaphylactic shock in hypersensitive patients). As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Progesterone 200 mg soft gelatin Capsules.
Any vaginal bleeding should always be investigated.

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme inducers
Drugs known to induce the hepatic CYP450-3A4 such as barbiturates, anti-epileptic agents (phenytoin, carbamazepine), rifampicin, phenylbutazone, bromcriptine, spironolactone, griseofulvin, some antibiotics (ampicillins, tetracyclines) and also herbal products containing St. John's wort, [Hypericum perforatum] may increase metabolism and the elimination of progesterone.

Enzyme inhibitors
Ketoconazole and other inhibitors of CYP450-3A4 such as ritonavir and nelfinavir may increase bioavailability of progesterone.
The metabolism of progesterone by human liver microsonmes was inhibited by ketoconazole (IC50< 0.1µ M).

Immunosuppressants
Progesterone may raise the plasma concentration of ciclosporin.

Antisteroidal drugs
Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic enzyme inducing effect.

Anticoagulants
Progesterone may enhance or reduce the anticoagulant effect of coumarins.
Progesterone antagonises the anticoagulant effect of phenindione.

Diabetic medications
An adjustment in anti-diabetic dosage may be required for women being treated concomitantly with progesterone.

Emergency contraceptives
The concomitant use of ulipristal acetate with progesterone is expected to result in reduced efficacy of progesterone.

Diazepam
Progesterone may increase the plasma concentration of diazepam.

Tizanidine
Progesterone may increase the plasma concentration of tizanidine.

Terbinafine
There have been occasional reports of breakthrough bleeding when terbinafine is used concomitantly with progesterone.

Laboratory tests
Progesterone may affect the results of laboratory tests of hepatic and/or endocrine functions.

4.6 Pregnancy and Lactation

Pregnancy
If pregnancy occurs during medication, Progesterone 200 mg soft capsules should be withdrawn immediately.
Clinically, data on a large number of exposed pregnancies indicate no adverse effects of progesterone on the foetus. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens + progesterone indicate no teratogenic or foetotoxic effect.
Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.

Lactation
Progesterone 200 mg soft gelatin Capsules is not indicated during breast-feeding.
Detectable amounts of progesterone enter the breast milk.

Fertility
As this medicinal product is indicated to support luteal deficiency in subfertile or infertile women, there is no deleterious known effect on fertility.

4.7 Effects on ability to drive and use machines

This medicine may cause drowsiness or dizziness; therefore care should be taken when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile
The reporting rate of adverse drug reactions with Progesterone Oral and Vaginal formulations was calculated as 1.43/1,000 patient year's corresponding to approximately 1.5 spontaneously reported cases in every 1000 patients exposed to Progesterone.

Tabulated list of adverse reactions
The information given below is based on extensive post marketing experience, primarily from oral administration of progesterone.
Adverse effects have been ranked under headings of frequency using the following convention: very common (≥ 1/10); common (≥ 1/100; <1/10); uncommon (≥ 1/1,000;<1/100); rare (≥ 1/10,000;<1/1,000); very rare

(<1/10,000); frequency not known (cannot be estimated from the available data).

Table 1: Tabulated adverse reactions following oral administration

System organ class	**Frequency Not Known (cannot be estimated from the available data)**
Gastrointestinal disorders	Abdominal pain Nausea
General disorders and administration site conditions	Fatigue
Nervous system disorders	Headache Somnolence Dizziness
Reproductive system and breast disorders	Vaginal haemorrhage
Skin and subcutaneous tissue disorders	Pruritus

Following vaginal administration, local intolerance (burning, itching or oily discharge) has been observed in clinical studies and has been reported in publications, but the incidence is extremely rare.
When used as recommended, transient fatigue or dizziness may occur within 1 – 3 hours of taking the medicine.
The information given below is based on extensive post marketing experience from vaginal administration of progesterone.
Adverse effects have been ranked under headings of frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Table 2: Tabulated adverse effects following vaginal administration

System organ class (SOC)	**Frequency Not known (cannot be estimated from the available data)**
Skin and subcutaneous tissue disorders	Pruritus
Reproductive system and breast disorders	Vaginal haemorrhage Vaginal discharge
General disorders and administrative site conditions	Burning sensation

Description of selected adverse effects
Somnolence or transient dizziness may occur 1 to 3 hours after intake of the drug. Bedtime dosing and reduction of the dose may reduce these effects.
The following risks apply in relation to systemic oestrogen/progestogen treatment:
Breast cancer risk
An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.

Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestogen combinations. The level of risk is dependent on the duration of use.

Endometrial cancer risk
Postmenopausal women with a uterus.
The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.
In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer.

Ovarian cancer
Use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed.

Risk of venous thromboembolism
HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT.

Risk of coronary artery disease
The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60.

Risk of ischaemic stroke
The use of oestrogen-only and oestrogen + progestogen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during the use of HRT.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms
High doses of progesterone may cause drowsiness, somnolence, or fatigue.
Treatment
Treatment of overdosage consists of discontinuation of Progesterone together with institution of appropriate symptomatic and supportive care.

5 Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action
Supplementation of the luteal phase
Progesterone is a natural progestogen, the main hormone of the corpus luteum and is the most important hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Utrogestan Vaginal 200mg Capsules have all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects.

Prevention of preterm birth
Progesterone is important during pregnancy in maintaining uterine quiescence by limiting the production of stimulatory prostaglandins responsible for uterine contractions. Progesterone also limits the release of matrix metalloproteinases that can cause cervical effacement and softening by inhibiting the expression of contraction-associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium.
Although levels of progesterone in the maternal circulation do not change significantly in the weeks preceding labour, the onset of labour at term and preterm is associated with a functional withdrawal of progesterone activity at the level of the uterus.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, micronised progesterone is absorbed by the digestive tract.
Pharmacokinetic studies conducted in healthy volunteers have shown that after oral administration of two 100 mg capsules (200mg), plasma progesterone levels increased to reach the Cmax of 13.8ng/ml +/- 2.9ng/ml in 2.2 +/- 1.4 hours. The elimination half-life observed was 16.8+/- 2.3 hours.

Although there were inter-individual variations, the individual pharmacokinetic characteristics were maintained over several months, indicating predictable responses to the drug.

Following vaginal administration, micronised progesterone is absorbed rapidly and achieves stable plasma levels in the range of 4-12 ng/ml, depending on the daily dose, and an average C_{max} at around the 8 hour mark is achieved with much less inter-subject variation than following oral administration.

Distribution
Progesterone is approximately 96%-99% bound to serum proteins, primarily to serum albumin (50%-54%) and transcortin (43%-48%).

Elimination
Urinary elimination is observed for 95% in the form of glycuroconjugated metabolites, mainly 3α, 5β–pregnanediol (pregnandiol).

Biotransformation
Progesterone is metabolised primarily by the liver.

Following oral administration, the main plasma metabolites are 20 α hydroxy- Δ 4 α- prenolone and 5 α-dihydroprogesterone. Some progesterone metabolites are excreted in the bile and these may be deconjugated and further metabolised in the gut via reduction, dehydroxylation and epimerisation. The main plasma and urinary metabolites are similar to those found during the physiological secretion of the corpus luteum.

Following vaginal administration, only low plasma levels of pregnanolone and 5α-dihydroprogesterone are detected, due to the lack of first-pass metabolism.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 Pharmaceutical Particulars

6.1 List of Excipients

Table 3: List of excipients

Name of ingredients	Grade	Used as
EXCIPIENTS FOR MEDICINE PREPARATION		
All-rac-Alpha-tocopherol	BP/Ph. Eur.	Antioxidant
Arachis oil	BP	Vehicle
Lecithin liquid	Pharma Grade	Emulsifying Agent
EXCIPIENTS FOR SOFT GELATIN CAPSULE SHELL		
Gelatin Bloom 200	USP-NF	Capsule shell former
Glycerin	USP	Plasticizer
Methyl Paraben	USP-NF	Preservative

Propyl Paraben	USP-NF	Preservative
Titanium Dioxide	USP	Opacifier
Purified Water	Ph. Eur. /BP	Vehicle
Mineral Oil	USP	Vehicle
Arachis oil	BP	Vehicle

6.1 Incompatibilities
Not applicable

6.2 Shelf-Life
Two (2) years from the date of manufacturing

6.3 Special Precautions for storage
Do not store above 30 °C. Store in the original package in order to protect from the moisture.

6.4 Nature and Content of container
Alu-PVC blister pack contains 10 capsule and IFC contains 3 blister packs.

6.5 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Marketing Authorization Holder
Renata Limited,
Plot # 1, Milk Vita Road,
Section - 7, Mirpur,
Dhaka -1216, Bangladesh.

Site of Manufacturing:
Renata Limited,
Rajendrapur Potent Product Facility
Noyapara, Bhawal Mirzapur, Rajendrapur,
Gazipur-1700, Bangladesh

8 Marketing Authorization Number
CTD10645

9 Date of first authorization/renewal of the authorization
30/05/2024

10 Date of revision of the text
06/05/2025