## 1.1 Summary Product Characteristics (SmPC)

### 1. Name of the Medicinal Product

GESTAGLEN 400 (Progesterone Soft Gelatin Capsules 400 mg)

### 2. Quantitative and Qualitative Composition:

Each soft gelatin capsules contains

| | | |
|---|---|---|
| Progesterone (Micronized) | BP | 400 mg |

For the full list of excipients, see Section 6.1.

### 3. Pharmaceutical Form:

Soft Gelatin Capsule

Cream coloured oval shaped soft gelatin capsules containing pale yellow oily paste.

### 4. Clinical Particulars:

#### 4.1 Therapeutic Indications

Progesterone Soft Gelatin Capsules 400 mg is indicated for the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of re current miscarriages.

#### 4.2 Posology and Method of Administration

Treatment should always be individualized to the patient. The decision to treat women who have experienced recurrent miscarriages should follow further investigation and is at the discretion of the clinician.

**Posology**

**Vaginal use .**

The recommended dose is 400 mg twice a day (morning and night). Treatment should be initiated during the first trimester of pregnancy, at first sign of vaginal bleeding and should continue to the 16th week of gestation.

**Paediatric population**

There is no relevant use of Progesterone Soft Gelatin Capsules 400 mg in the paediatric population.

**Elderly patients**

There is no relevant use of Progesterone Soft Gelatin Capsules 400 mg soft vaginal capsules in the elderly.

**Method of administration:** For oral/Vaginal use.

Oral

Capsules should be taken at bedtime on an empty stomach.

Vaginal

Each capsule must be inserted deep into the vagina.

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

**4.3 Contraindications**

***Oral and vaginal administration:***

- Hypersensitivity to the active substance or to any of the excipients used.
- Acute porphyrias
- Avoid in patients with a history of liver tumours
- Breast cancer (unless progestogens are being used in the management of this condition)
- Genital cancer (unless progestogens are being used in the management of this condition)
- History during pregnancy of idiopathic jaundice
- History during pregnancy of pemphigoid gestationis
- History during pregnancy of severe pruritus  History of thromboembolism.
- Incomplete miscarriage
- Missed miscarriage
- Severe arterial disease
- Thrombophlebitis
- Undiagnosed vaginal bleeding
- Cerebral haemorrhage

- Breast-feeding

**4.4 Special warnings and precautions for use**

A complete medical examination must be performed before starting the treatment and regularly during the treatment.

Progesterone Soft Gelatin Capsules 400 mg should only be used for threatened miscarriage during the first trimester; up tothe 16$^{th}$ week of pregnancy and must only be administered by the vaginal route.

Progesterone Soft Gelatin Capsules 400 mg is not suitable as a contraceptive.

Treatment should be discontinued upon diagnosis of a missed abortion.

**4.5 Interaction with other medicinal products and other forms of interaction**

Progesterone soft gelatin capsules may interfere with the 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.

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole and other inhibitors. Ketoconazole ($IC_{50}$ <0.1 µM) is a known inhibitor of cytochrome P450 3A4. These data therefore suggest that ketoconazole may increase the bioavailability of progesterone. The clinical relevance of the *In-vitro* findings is unknown.

Progesterone may raise the plasma concentration of ciclosporin.

Progesterone may increase the plasma concentration of diazepam & tizanidine. Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic

enzyme-inducing effect. Progesterone may enhance or reduce the anticoagulant effect of coumarins. Progesterone antagonises the anticoagulant effect of phenindione. An adjustment in anti-diabetic dosage may be required for women being treated concomitantly with progesterone. The concomitant use of ulipristal acetate with progesterone may result in reduced efficacy of progesterone. There have been occasional reports of breakthrough bleeding when terbinafine is used concomitantly with progesterone.

Progesterone soft gelatin capsules may affect the results of laboratory tests of hepatic and/or endocrine functions.

**4.6 Fertility, Pregnancy and Lactation**

***Pregnancy***

No association has been found between the maternal use of natural progesterone in early pregnancy and foetal malformation.

**Breast-feeding**

Progesterone Soft Gelatin Capsules 400 mg is not indicated during breast-feeding.

Detectable amounts of progesterone enter the breast milk.

***Fertility:***

As this medicinal product is indicated to prevent miscarriage in women, there is no known deleterious effect on fertility.

**4.7 Effects on Ability to drive and use machines**

Oral Administration of Progesterone capsules may cause drowsiness or dizziness in a minority of patients. Therefore caution should be taken when driving or using machines. These problems can be avoided by taking the capsules at bedtime

**4.8 Undesirable Effect**

Local intolerance (burning, itching or oily discharge) has been observed, but the incidence is extremely rare.

When used as recommended, transient fatigue or dizziness may occur within 1 – 3 hours of taking the medicine.

| **Undesirable effects** | | | | | |
|---|---|---|---|---|---|
| **S. No.** | **System organ class** | **Common ≥1/100; <1/10** | **Uncommon ≥1/1000; <1/100** | **Rare ≥1/10 000; <1/1,000** | **Very rare <1/10,000** |
| **1.** | **Reproductive system and breast disorders** | Irregular menstruation, Amenorrhoea, metrorrhagie | Mastodynia | | |
| **2.** | **Central nervous system disorders** | Headaches | Drowsiness, Fleeting dizzy sensations | | Depression |
| **3.** | **Gastrointestinal disorders** | | Vomiting, Diarrhoea, Constipation | Nausea | |
| **4.** | **Hepatobiliary disorders** | | Cholestatic jaundice | | |
| **5.** | **Immune system disorders** | | | Anaphylactic reactions | Urticaria |
| **6.** | **Skin and subcutaneous tissue disorders** | | Pruritus Acne | | Chloasma |

**Reporting of suspected adverse reactions:** Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting System (PvERS)

### 4.9 Overdose

Symptoms of over dosage may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.

## 5. Pharmacological Properties:

## 5.1 Pharmacodynamic properties

***Pharmacotherapeutic group:***

Sex hormones and modulators of the genital system, progestogens

***ATC code:*** G03DA04

***Mechanism of action***

Progesterone is a natural endogenous 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. Progesterone Soft Gelatin Capsules 400 mg has all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular has a gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects.

The pharmacodynamic effects for threatened and recurrent miscarriage are that progesterone modulates maternal immune responses to protect the foetus, improves the utero-placental circulation, maintains cervical integrity throughout pregnancy, promotes myometrial relaxation, inhibits prostaglandin production, and possesses anti-inflammatory properties.

**Clinical efficacy/safety studies**

The efficacy and safety of micronized progesterone in preventing miscarriage in women, with dual risk factors of early pregnancy bleeding and previous history of miscarriages, was evaluated in the PRISM study. The benefit of treatment with vaginal progesterone 400 mg twice daily increased with an increasing number of prior miscarriages. The benefit reached statistical significance in the pre specified subgroup of women with three or more previous miscarriages and current pregnancy bleeding; live birth rate was 72% (98/137) with progesterone vs 57% (85/148) with placebo (rate difference 15%; risk ratio, 1.28, 95% CI, 1.08-1.51; P=.004). For this group, the number needed to treat was 8 (95% CI,7-10). From a safety perspective, progesterone 400 mg was well tolerated.

## 5.2 Pharmacokinetic properties

Progesterone Soft Gelatin Capsules 400 mg provides a local effect on the vagina and uterus. The efficacy of vaginal progesterone is related to the overall amount of progesterone accumulating in the endometrium and not to the amount that is systemically absorbed.

***Absorption***

Following oral administration, Micronized progesterone is absorbed by the digestive tract. Pharmacokinetic studies conducted in healthy volunteers have shown that after oral administration of two 100 mg capsules (200 mg), 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.

Micronised progesterone is rapidly absorbed following vaginal administration. Unlike oral progesterone, vaginal progesterone does not undergo first pass metabolism in the gastrointestinal tract and liver. As a result of the "uterine first pass effect", relatively high concentrations occur in uterine and nearby tissues with low systemic exposure to progesterone and its metabolites.
The plasma exposure following administration of different vaginal dosages (e.g. 200 mg to 600 mg) is non-linear and increase less than proportional to dose. In a reported clinical study, administration of an 600 mg daily vaginal dose of progesterone resulted in stable plasma concentrations throughout administration times with the highest average plasma concentration equal to around 11.6 ng/ml.

***Distribution***

The small amount of progesterone that is absorbed is transported via the lymph and blood vessels and approximately 96 - 99% is bound to serum proteins, mainly into serum albumin (50 - 54%) and transcortin (43 - 48%).

Vaginally accumulated progesterone undergoes the first metabolic cycle in the uterus, causing higher hormone levels in the uterus and nearby tissues.

***Biotransformation***

Following oral administration, the main plasma metabolites are 20 α hydroxy-Δ4α- prenolone and 5α-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.

***Elimination***

Progesterone undergoes renal and biliary elimination. 95% of systemically absorbed progesterone is eliminated from the urine as glucuronide conjugated metabolites.

**5.3 Preclinical Safety Data**

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology and toxicity

## 6. Pharmaceutical particulars

**6.1 List of Excipients**

Arachis oil, Lecithin Liquid, Gelatin (160 Bloom), Glycerin, Titanium Dioxide and Purified Water are the excipients used in this formulation

**6.2**

**Incompatibilities:**

Not applicable

**6.3 Shelf Life:**

36 months.

**6.4 Special Precaution for Storage:**

Store below 30°C. Store in the original packaging in order to protect from light. Keep out of reach of children.

**6.5 Nature and composition of container:**

Clear PVC-Aluminium Blister. (3 x 10 Capsules)

**6.6 Instructions for use/handling** No special requirements

**6.7 Special precautions for disposal and other handling** Not applicable

**7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES**

**Marketing Authorization Holder**

Glenmark Pharmaceuticals Ltd.
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**Manufacturer Registered Office:**

M/s. Steril-Gene Life Sciences (P) Ltd,
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**Manufacturing Facility:**

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No: 45, Mangalam Main Road,
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**8. Marketing Authorization Number**

CTD9766

**9. Date of first registration**

21st May,2026

**10.Date of revision of the text**

21st May,2026