Summary Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

GESTAGLEN 200 CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft gelatin capsule contains:
Progesterone (Natural Micronised) BP ..... 200 mg
Approved colours used in capsule shells.

3. PHARMACEUTICAL FORM

Soft Gelatin Capsule

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

Vaginal or oral administration: Disorders related to progesterone deficit in particular menopause (in association with estrogen therapy).

Vaginal administration: Progesterone substitution for ovary deprived women in situation of total progesterone deficiency.

Supplementation of the luteal phase during in vitro fertilization cycles. Supplementation of the luteal phase during spontaneous or induced cycles, in cases of hypofertility or primary or secondary ovarain failure, particulary through dysovulation. In cases of threatning abortion or prevention of repeated abortions due to proven luteal insufficiency. For all other progesterone indications, in the case of: Adverse events due to progesterone, contraindication of the oral route of administration hepatopathy.

4.2 Posology and Method of Administration

The recommended dosages should be strictly observed. Whatever the indication and route of administration (oral or vaginal), the dosage should never exceed 200mg per dose.

Oral administration

This medicinal product should be taken on an empty stomach preferably in the evening before going to bed. Usually, the dosage is 200 to 300 mg of progesterone daily in two intakes: one in the morning, preferably 2 hours after breakfast, another one to two in the evening (at bedtime) , on an empty stomach.

In luteal insufficiency (premenstrual syndrome, benign mastopathy, menstrual irregularities), dose is from 200 to 300 mg daily:

- either 200 mg in one intake at bedtime,

– or 300 mg in two intakes.
for 10 days per cycle, usually from the 17th to the 26th day, inclusive.

For the pre menopause: the dose is 300 mg daily, divided into two intakes, i.e., 100 mg preferably two hours after breakfast and 200 mg at bedtime for 10 days (from the 17th to the 26th day of the cycle) up to 20 days (from the 7th to the 26th day of the cycle).

For menopause (HRT): Isolated therapy is not recommended (risk of endometrial hyperplasia). Progesterone is therefore combined at a dose of 200 mg . The usual dose is 200 mg daily for 12 to 14 days per month, if the patient does not wish to have regular cyclic bleeding. The total daily dose should be taken at bedtime in conjunction with estrogen administered at the lowest effective dose (i.e. that which induces a mean E2 plasma level above 60 pg/ml). The great majority of patients will become amenorrheic during the first year of treatment.

This treatment must be followed by the total discontinuation of any replacement therapy for approximately one week during which a deprivation hemorrhage is often observed. If the patient wishes to have regular cyclic bleeding, the dose is 300 mg daily for 10 days per month, divided into two intakes, i.e. 100 mg in the morning and 200 mg at bedtime. The estrogen dose has to be increased (i.e. 3 mg percutaneous 17β estradiol per day).

In these indications the vaginal route is used, at the same dosages as the oral route, in cases of side effects due to progesterone (drowsiness after oral absorption).

Vaginal administration: The woman should insert each capsule deep into the vagina. On the average, the dosage is 200 mg of progesterone daily distributed into two doses: one in the morning, another one in the evening. In case of partial luteal insufficiencies (dysovulation, menstrual irregularities), the treatment should be carried out during 10 days per cycle, usually from the 17th to the 26th day, on the basis of 200 mg per day.

Progesterone substitution of ovary deprived women during complete deficiency (donation of ovocytes): progesterone dose is 100 mg on the 13th and 14th days of the transfer cycle, then 200 mg per day 15th to the 25th day of the cycle in one or two intakes. From the 26th day, the dose is increased in case of onset of pregnancy by 100 mg per day each week reaching a maximum of 600 mg per day divided into 3 intakes. This dosage will be continued until the 60th day and until the 12th week of pregnancy and no further.

Supplementation of the luteal phase during IVF, 400 mg-600 mg per day, in two to three divided doses, starting on the evening of the HCG injection until the 12th week of pregnancy.

During the threat of abortion or prevention of repeated abortion due to luteal insufficiency, the recommended dose is 200 mg to 400 mg per day in 2 intakes until the 12th week of amenorrhea and no further.

Supplementation of the luteal phase during spontaneous or induced cycles, in cases of hypofertility or primary or secondary sterility, particularly through dysovulation. The recommended posology is from 200 mg to 300 mg per day in two intakes, from the 17th day of the cycle during 10 days. The treatment must be repeated, as soon as possible, in the case of amenorrea and diagnosis of pregnancy until the 12th week of pregnancy.

Method of administration: For oral/Vaginal use.

4.3 Contraindications

Oral and vaginal administration:

Severe liver disease if the results of liver function tests have failed to return to normal), hepatic cell tumors, rotor syndrome and Dubin-Johnson syndrome;

- Hypersensitivity to progesterone or to any of the excipients listed below section.
- Thrombophlebitis, thromboembolic disorders, cerebral hemorrhage, or history of these conditions
- Carcinoma of the breasts
- Suspected or confirmed breast or genital organ neuplasia
- Undiagnosed vaginal bleeding.

Conditions of rare occurrence known to be affected by sex hormones, or a history of these conditions (the condition may have occurred first or worsened during pregnancy or use of sex hormones), i.e., herpes gestationis, jaundice of pregnancy, otosclerosis, severe pruritus, or porphyria

4.4 Special warnings and precautions for use

The treatment under recommended conditions is not contraceptive.

If the treatment sequence is started too early in the month, particularly before the 15th day of the cycle, the cycle may be shortened and/or bleeding may occur.

More than a half of the early spontaneous abortions are due to genetic complications. Besides, infectious manifestations and mechanical disorders may be responsible for premature abortions.

The only effect of progesterone administration would then be a delay in the evacuation of the dead egg or interruption of a non-progressive pregnancy.

Progesterone application should be restricted to cases of corpus luteum deficiencies.

- If uterine bleeding is present, do not prescribe before establishing a cause, particularly with endometrial investigations.
- Because of the metabolic risks and risks of thromboembolism which cannot be entirely excluded, administration should be discontinued in the event of:

  - ✓ eye disorders such as reduced vision, diplopia and retinal vascular lesions;
  - ✓ venous thromboembolic or thrombotic events, regardless of territory;
  - ✓ severe headaches
  - ✓ Patients should be monitored closely if they have a past history of venous thrombosis.
  - ✓ If a patient develops amenorrhoea during treatment, ensure that she is not pregnant.

Progesterone capsules should only be used in pregnancy during the first trimester and only by the vaginal route. Progesterone capsules are not a treatment of threatening premature labour. The use of micronised progesterone during the second and third trimesters of pregnancy can lead to the development of cholestatic jaundice of pregnancy or hepato-cellular liver disease.

Cases of hepatic cytolysis and cases of cholestasis or pregnancy have been reported in exceptional cases during administration or micronized progesterone during the 2nd and 3rd trimesters of pregnancy.

Progesterone capsules contains soya lecithin and may cause hypersensitivity reactions (urticaria and anaphylactic shock).

Precautions:
Oral administration
Somnolence or dizziness may occur 1-3 hours after ingestion of Progesterone capsules. If these symptoms are severe, at a dose of 300 mg per day, it should be reduced to 200 mg (at bedtime). In most cases, side effects can be avoided by taking the 200 mg dose at bedtime, which has the additional advantage of a favorable effect on sleep. In case of HRT, it is recommended to check that the estrogens are administered at sufficient doses.

Oral and vaginal administration

- During prolonged treatment with progesterone, periodic medical examinations are recommended, including hepatic function.
- Treatment should be discontinued if the results of liver function tests become abnormal or if cholestatic jaundice appears.
- Chloasma is occasionally seen during the use of estrogen and/or progestagen-containing preparations, especially in women with a history of chloasma gravidarum. In women with a tendency to chloasma, exposure of the skin to natural or artificial sunlight may induce or aggravate the condition.
- Patients with cardiovascular diseases (or history of this condition) should be kept under close medical supervision, since with estrogen/progestagen containing oral contraceptive preparations a slightly increased risk of some cardiovascular disorders have been reported. However, with natural progesterone, there are no indications of such increased risks.
- Fluid retention may occur; therefore, conditions influenced by this factor (hypertension,epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.
- Depression: observe patients who have a history of psychic depression and discontinue the drug if the depression recurs to a serious degree.

4.5 Interaction with other medicinal products and other forms of interaction

Oral administration: Combination with other medicinal products may decrease progesterone metabolism which may alter its effect.

Oral and Vaginal administration:

- Prolonged concurrent use (over three months) of barbiturates, carbamazepine, hydantoins, anti-epileptics (phynytoin), phenylbutazone, spironolactone, griseofulvin or rifampicin with Progesterone capsules can result in clinically relevant interactions. Probably these compounds decrease the effectiveness of Progesterone capsules by increasing the hepatic metabolism.
- Some antibiotics (ampicillins, tetracyclines): changes in the intestinal flora leading to a change in the steroid enterohepatic cycle. As these interactions may vary between people, the clinical results are not necessarily predictable.

Although data are limited, it is considered possible that activated charcoal and griseofulvin may decrease the effectiveness of Progesterone capsules. Progesterone capsules may possibly increase the therapeutic, pharmacologic, or toxicologic effects of cyclosporin, theophyllines and troleandomycin.

The bioavailability of progesterone may be reduced by smoking and increased by alcohol abuse. The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 <0.1 µM Ketoconazole 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.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Use of this medicine is not contraindicated during pregnancy. However, there is evidence of potential harm to the fetus (especially male fetus) during the first 4 months of pregnancy. Use during pregnancy is not recommended during the first 4 months; moreover, the use of this medicine during the second and third trimesters can lead to the development of hepatic diseases.

No relation between progesterone and foetal malformations has been observed during numerous epidemiologiocal studies on more than a thousand patients.

Lactation:

There are insufficient data on the use of progesterone during lactation to assess potential harm. Progesterone passes into the breast milk. It should therefore be avoided in women whilst they are breast-feeding.

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 Effects

Oral administration:

Undesirable effects					
S.No:	**System organ class**	**Common undesirable effects ≥1/100; <1/10**	**Uncommon undesirable effects ≥1/1000; ≤1/100**	**Rare undesirable effects ≥1/10 000; ≤1/1 000**	**Very rare undesirable effects ≤1/1000 0**
1	**Reproductive system and breast disorders**	Altered periods. Amenorrhoea. Intercurrent bleeding	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**				Urticaria
6	**Skin and subcutaneous tissue disorders**		. Pruritus . Acne		Chloasma

Drowsiness, somnolence and/or fleeting dizzy sensations are seen particularly with concomitant hypo estrogenism. These effects disappear immediately without compromising the benefit of treatment when doses are reduced or higher estrogen levels are restored.

If the treatment sequence is started too early in the month, particularly before the 15th day of the cycle, the cycle may be shortened or intercurrent bleeding may occur. Changes in periods, amenorrhoea or intercurrent bleeding have been observed and associated with the use of progesterones in general.

Rashes, fluid retention, weight changes, changes in libido, premenstrual symptoms, pyrexia, insomnia, alopecia, hirsutism; rarely jaundice.

Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. Vaginal administration Despite the possibility of local irritation (soya lecithin), No local intolerance was observed (such as pruritis, irritation, itching or greasy discharge) during different clinical trials.

No general adverse effects, in particular, somnolence or dizziness, were observed at recommended dosages during clinical trials. This may be attributed to the absence of certain metabolite increase after its vaginal administration.

4.9 Overdose

Oral administration

The usual dosage may prove to be excessive in certain patients.

- Either because of the persistence or reappearance of unstable Endogenic secretion of progesterone,
- Or because of particular sensitivity to the Product (see "pharmacoKinetics"). In such cases, one should reduce the dosage quantitatively or change the rhythm:
- Somnolence, transient dizziness: 200 mg at bedtime from the 12th to the 14th day of cycle or vaginal administration.

- Shortening of the cycle or breakthrough bleeding: take the treatment later in the cycle (for instance, from the 19th day of the cycle instead of the 17th).
- Check that estradiol concentrations are sufficient in the perimenopausal period and in hormone replacement therapy for the menopause. Symptoms that may arise are: nausea, vomiting, somnolence and dizziness. In case of marked sedation, symptomatic treatment can be given. Vaginal administration Up to now, no overdose was observed in this method of administration.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
urinogenital system and sex hormones

ATC code: G03DA04

Mode of action
Progesterone is a natural progestative agent, the standard hormone of the family of progestative agents.

It possesses the set of properties characterizing natural progesterone, namely, antiestrogenic, slightly antiandrogenic, antialdosterone, gestagen.

Micronized progesterone is capable of inducing dose-dependent secretory changes in the endometrium, such as pseudo-stratification and basal vacuolation of glycogen. In addition, micronized progesterone exerts antiproliferative or anti-mitotic effects on the endometrium, e.g., suppression of nuclear estradiol receptors, suppression of DNA synthesis, and induction of 17β- Estradiol and isocitric dehydrogenase activities.

In part of the patients (depending on the estrogen-progesterone dose regimen) Micronized progesterone treatment does not lead to complete secretory transformation of the endometrium, and often there is no withdrawal bleeding. However, this lack of complete transformation and cyclic bleeding is no cause for concern about endometrial hyperplasia since micronized progesterone fully suppresses mitotic activity in the endometrial glandular cells after 12 days of administration (200 mg or 300 mg daily dose).

With regard to metabolic side-effects and safety, micronized progesterone has anti-mineralocorticoid effects upon the urinary sodium excretion. Accordingly, in hypertensive patients a slight reduction in blood pressure has been observed.

Unlike synthetic progestagens, micronized progesterone capsules exert no significant effects on haemostasis, blood pressure (in normotensive subjects), body weight carbohydrate metabolism, lipid and lipoprotein metabolism, bone or calcium metabolism, and liver function. The preparation also has little or no effect on the plasma levels of cortisol, estrone, estradiol, FSH, LH, prolactin, adrenalin, noradrenalin, androstenedione, aldosterone and a weak antiandrogen activity.

Micronized progesterone is capable of correcting the capillary permeability in patients with orthostatic idiopathic oedema.

Oral administration of progesterone induces an increase in unconjugated pregnandiol and pregnanolone plasma values, two metabolites with possible anaesthetic effects. This probably explains the transient drowsiness or dizziness which may occur in certain patients, especially after ingestion of 200 mg dose or more, while fasting.

Vaginal progesterone, at usual dosage, allows reaching and maintaining plasmatic progesterone levels stable and similar to that achieved during the luteal phase of a normo-ovulatory cycle and in this way a full endometrial maturation adequate for a possible embryo implantation. When given at progressively increased dosages, vaginal progesterone allows reaching plasmastic progesterone levels similar to that observed during the first pregnancy trimester.

After vaginal administration, a greater amount of progesterone is retained in the genital tractus. The vaginal absorption is rapid and allows by-pass of the hepatic first pass metabolism. The metabolic pathways after vaginal administration is different so that less 5β pregnanolone is produced No side effects were observed in the vaginal route of therapy.

5.2 Pharmacokinetic properties

Oral administration

Absorption

Micronized progesterone is absorbed by the digestive tract. Plasmatic progesterone levels increase from the first hour, and the highest plasmatic levels are observed 1 to 3 hours after administration.

Pharmacokinetic studies carried out with volunteers have shown that after a simultaneous ingestion of two capsules of Utrogestan 100, the mean plasmatic progesterone concentration increases from 0.13 ng/ml to 4.25 ng/ml after 1 hour, to 11.75 ng/ml after 2 hours, to 8.37 ng/ml after 4 hours, to 2.00 ng/ml after 6 hours, and to 1.64 ng/ml after 8 hours.

Taking into account the tissue retention time of the hormone, it seemed necessary to divide the dose into two applications, about 12 hours between one another, in order to achieve impregnation through all day.

Although there are considerable individual variations, any individual preserves the same pharmacokinetic characteristics for several months, enabling individual adaptation of the dosage.

Metabolism
The main metabolites in the plasma are 20-α-hydroxy-Δ-4α pregnanolone and 5-α dihydroprogesteron. Urinary elimination is observed in 95% of cases in the form of glycuroconjugate metabolites, mainly 3-α-5-β-pregnandiol. These plasmatic and urinary metabolites are similar to those found during the physiological secretion of the ovarian corpus luteum.

Vaginal administration
Absorption
Progesterone administered vaginally is absorbed rapidly since high plasma levels of progesterone are observed after one hour. The maximal plasma concentration of progesterone is reached within 2 to 6 hours after the application and remains at mean concentration of 9.7 ng/ml over 24 hours, after administration of 100 mg in the morning and in the evening.

This mean recommended dosage therefore induces steady physiological plasma concentrations of progesterone, similar to those observed during the luteal phase of a normal ovulatory cycle allowing induction of an adequate maturation of the endometrium which is favorable for the possible embryo implantation. The weak inter-individual variations of the progesterone levels enable one to anticipate the reactions expected with a standard posology. With doses superior to 200 mg daily, the progesterone concentrations are similar to those of the first trimester of pregnancy.

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. Protect from light and moisture. 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:

M/s. Steril-Gene Life Sciences (P) Ltd,
No: 45, Mangalam Main Road,
Mangalam Village, Villianur Commune,
Puducherry – 605 110,
India

8. MARKETING AUTHORIZATION NUMBER

H2016/CTD4569/415

9. DATE OF FIRST REGISTRATION/RENEWAL OF A PRODUCT LICENSE

19.02.2009

10. DATE OF REVISION OF THE TEXT

04.08.2026