Product Summary

1. Name of the medicinal product
I-Gest SR 200®

2. Qualitative and quantitative composition
Each film coated tablet contains
Progestrone IP 200 mg

3. Pharmaceutical form
Oral tablet with natural micronised progesterone in a sustained release form

4. Clinical particulars
4.1 Therapeutic indications
• Premenstrual syndrome
• Menstrual irregularities through dysovulation or anovulation
• Menopause (in addition to oestrogen treatment) to significantly reduce the risk of endometrial hyperplasia and carcinoma.
• Dysfunctional uterine bleeding (DUB)
• Secondary amenorrhoea
• Luteal support during assisted reproductive techniques (ART)
• Luteal support in in luteal phase defect

4.2 Posology and method of administration
• Premenstrual syndrome, menstrual irregularities: The treatment should be started at a dose of 200 to 300 mg per day, 10 days per cycle, usually from the 14th day to until onset of menstruation.
• Menopause (in addition to oestrogen treatment): 200 mg per day in the evening for the last 14 days of the oestrogen treatment per cycle (i.e. from day 8 to day 21
for a 28-day cycle; and from day 12 to day 25 for a 30-day cycle).
• DUB: 300 to 400 mg (orally) once daily from the 12th day of the cycle for 10 days.
• Secondary amenorrhoea: May be given as a single daily dose of 400 mg at bedtime for 10 days.
• Luteal support during assisted reproductive techniques: 400 mg once a day from the day of embryo transfer till pregnancy is confirmed. If pregnant, it should be continued till the 12th week of pregnancy.
• Luteal support in luteal phase defect: 300 mg from the 17th day of cycle for 10 days. If pregnant, it should be continued till the 12th week of pregnancy.

The tablet is to be administered at bedtime.

4.3 Contraindications
Micronized progesterone sustained-release tablets should not be used in women with any of the following conditions:
• In patients with a known hypersensitivity to its ingredients.
• Undiagnosed abnormal genital bleeding.
• Known, suspected, or a history of breast cancer
• Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
• Active arterial thromboembolic disease (e.g. stroke and myocardial infarction), or a history of these conditions.
• Known liver dysfunction or disease.

4.4 Special warnings and precautions for use
Cardiovascular Disorders
An increased risk of pulmonary embolism, deep vein thrombosis (DVT), stroke and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with progestin therapy should be discontinued immediately.
Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or thromboembolism (e.g., personal history or family history of venous thromboembolism (VTE), obesity and systemic lupus erythematosus) should be managed appropriately.
**Malignant Neoplasms**

**Breast cancer**
The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations. In addition, mammography examinations should be scheduled based on patient's age, risk factors and poor mammogram results.

**Endometrial Cancer**
Clinical surveillance of all women using estrogen plus progestin therapy is important. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

**Ovarian Cancer**
Estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be permanently discontinued.

**Fluid Retention**
Progesterone may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal dysfunction warrant careful observation.

**Dizziness and Drowsiness**
Natural micronized progesterone in sustained release formulation may cause transient dizziness and drowsiness and should be used with caution when driving a motor vehicle or operating machinery.
Should be taken as a single daily dose at bedtime.
The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.
Discontinue medication pending an examination if there is sudden, partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If the examination reveals papilloedema or retinal vascular lesions, natural micronized
progesterone should be withdrawn.

Natural micronized progesterone contains the hormone, progesterone, which is present in significant concentrations in women during the second half of menstrual cycle and during pregnancy. This should be borne in mind when treating patients with conditions that may be hormone-sensitive.

The pre-treatment physical examination should include special reference to the breasts and pelvic organs, as well as the Papanicolaou smear.

Because progesterone may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In cases of breakthrough bleeding, as in any cases of irregular vaginal bleeding, non-functional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Patients who have a history of clinical depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Although concomitant use of conjugated oestrogen and micronized progesterone tablets did not result in a decrease in glucose tolerance, diabetic patients should be carefully observed while receiving oestrogen-progestin therapy.

It should be noted that, particularly in case of people who drive vehicles or operate machines, there is a risk of drowsiness or giddiness associated with the use of natural micronized progesterone.

Rare instances of syncope and hypotension of possible orthostatic origin have been observed in patients taking micronized progesterone tablets.

More than half of the spontaneous premature abortions are due to genetic abnormalities. Further, infectious phenomena and mechanical troubles can be responsible for abortions.

**Renal impairment**

No formal studies have evaluated the effect of renal disease on the disposition of progesterone. Since progesterone metabolites are eliminated mainly by the kidneys, micronized progesterone tablets should be used with caution and only with careful monitoring in patients with renal dysfunction.
Hepatic impairment
No formal studies have evaluated the effect of hepatic disease on the disposition of progesterone. However, since progesterone is metabolized by the liver, use in patients with severe liver dysfunction or disease is contraindicated. If treatment with progesterone is indicated in patients with mild-to-moderate hepatic dysfunction, these patients should be monitored carefully.

Paediatric use
Should not be used in children.

4.5 Interaction with other medicinal products and other forms of interaction
Ketoconazole or other known inhibitors of the cytochrome P4503A4 enzyme may increase the bioavailability of progesterone.

4.6 Pregnancy and lactation
Natural micronized progesterone in sustained release formulation can be used when clearly indicated. The administration of natural micronized progesterone in the course of the second and third trimester of pregnancy can favour the appearance of severe cholestasis or hepatitis. Reproductive studies performed in mice reveal little or no evidence of impaired fertility or harm to the foetus due to progesterone. Rare cases of congenital anomalies, including cleft palate, cleft lip, ventricular septal defect, patent ductus arteriosus and other congenital heart defects, have been reported in the infants of women using micronized progesterone in early pregnancy. Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins. The effect of this on the nursing infant has not been determined. Hence, caution should be exercised when micronized progesterone tablets are administered to a nursing mother.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects
The menstrual cycle may be shortened or there may be inter-menstrual bleeding. Menstruation may occur earlier than expected or, more rarely, menstruation may be
delayed. In case of shortening of the menstrual cycle or intermittent bleeding, shift the initiation of treatment to a later date (e.g. the 19th day of the cycle instead of the 17th day).

Adverse experiences reported were headache, breast pain, breast tenderness, joint pain, depression, dizziness, drowsiness or giddiness, abdominal pain, fatigue, abdominal distension, abnormal bloating, hot flashes, nausea, vomiting, emotional liability and irritability.

In clinical trials in patients with secondary amenorrhoea, overall, the most frequently reported treat-emergent adverse reactions, reported in greater than or equal to 5% of subjects, were nausea, fatigue, vaginal mycosis, nasopharyngitis, upper respiratory tract infection, headache, dizziness, breast tenderness, abdominal distension, acne, dysmenorrhoea, mood swing and urinary tract infection.

The following additional adverse reactions have been reported with micronized progesterone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure:

**Genitourinary System:** endometrial carcinoma, hypospadias, intra-uterine death, menorrhagia, menstrual disorder, metrorrhagia, ovarian cyst, spontaneous abortion.

**Cardiovascular:** circulatory collapse, congenital heart disease (including ventricular septal defect and patent ductus arteriosus), hypertension, hypotension, tachycardia.

**Gastrointestinal:** acute pancreatitis, cholestasis, cholestatic hepatitis, dysphagia, hepatic necrosis, hepatitis, increased liver function tests (including alanine aminotransferase increased, aspartate aminotransferase increase, gamma-glutamyltransferase increased), jaundice, swollen tongue.

**Skin:** alopecia, pruritus, urticaria.

**Eyes:** blurred vision, diplopia, visual disturbance.

**Central Nervous System:** aggression, convulsion, depersonalization, depressed, consciousness, disorientation, dysarthria, loss of consciousness, paraesthesia, sedation, stupor, syncope (with and without hypotension), transient ischemic attack, suicidal ideation.

During initial therapy, a few women have experienced a constellation of many or all of the following symptoms: extreme dizziness and/or drowsiness, blurred vision, slurred speech, difficulty walking, loss of consciousness, vertigo, confusion, disorientation, feeling drunk and shortness of breath.
**Miscellaneous:** abnormal gait, anaphylactic reaction, arthralgia, blood glucose increased, choking, cleft lip, cleft palate, difficulty walking, dyspnoea, face oedema, feeling abnormal, feeling drunk, hypersensitivity, asthma, muscle cramp, throat tightness, tinnitus, vertigo, weight decreased, weight increased.

### 4.9 Overdose

Although no studies on overdosage have been conducted in humans and there is a wide margin of safety with progesterone, overdosage may produce euphoria or dysmenorrhoea. In the case of overdosage, micronized progesterone sustained-release tablets should be discontinued and the patient should be treated symptomatically.

### 5. Pharmacological properties

#### 5.1 Pharmacodynamic properties

Progesterone is lipophilic in nature and diffuses freely into cells, where it binds to the progesterone receptors and exerts its progestational activity. The steroid receptor complex binds to DNA in the nucleus, thereby inducing the synthesis of specific proteins. Progesterone receptor concentrations are low in the absence of oestrogens and increase following oestrogen administration.

Progesterone is a naturally occurring steroid that is secreted by the ovaries, placenta and adrenal glands. In the absence of adequate oestrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual tissue, and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

Normal or near-normal endometrial responses to oral oestradiol and intramuscular progesterone have been noted in functionally agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory levels of gonadotropins.

#### 5.2 Pharmacokinetic properties

**Absorption**

When administered by the oral route, the micronized progesterone is absorbed
through the digestive tract. Serum progesterone concentrations are linear and dose-proportional following multiple-dose administration of progesterone. The oral bioavailability of progesterone is increased through micronization.


Study Design: 12 postmenopausal women were randomized to receive either placebo or 300 mg tablets of Oral Micronized Progesterone Sustained Release Tablets progesterone daily for two weeks. Multiple blood samples over time were analyzed for serum progesterone concentrations. Standard pharmacokinetic parameters were calculated.

Results & Conclusion: Steady state concentrations were reached by the fourth day. Pharmacokinetic parameters of Oral Micronized Natural Progesterone Sustained Release Tablets revealed serum progesterone concentration in the luteal phase range with once a day dosing.

Serum progesterone concentration over first 24 hours after oral ingestion placebo or 300 mg Sustained release natural progesterone.

Serum progesterone concentration over last 24 hours (day 15) after oral ingestion of placebo or 300 mg Sustained release natural progesterone after two weeks therapy.
Mean trough serum progesterone concentrations obtained over two weeks in subjects taking placebo or 300 mg of Sustained release natural progesterone.

**Distribution**

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

**Metabolism**

Progesterone is metabolized primarily by the liver, largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulphate metabolites. Progesterone metabolites, which are excreted in the bile, may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation and epimerization.

**Excretion**

The glucuronide and sulphate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites are eliminated mainly by the kidneys. Progesterone metabolites, which are excreted in the bile, may undergo enterohepatic recycling or may be excreted in the faeces.

The pharmacokinetics of natural micronized progesterone in sustained release formulation has not been assessed in low body weight or obese patients.

**5.3 Preclinical safety data**

Not applicable.
6. Pharmaceutical particulars

6.1 List of excipients
Titanium dioxide IP.
Excipients q.s

6.2 Incompatibilities
None known.

6.3 Shelf life
24 Months.

6.4 Special precautions for storage
Store protected from light and moisture, at a temperature not exceeding 30°C.

Administrative data

7. Marketing authorisation holder
Strides Shasun Limited
Strides House, Bilekahalli,
Bannerghatta Road,
Bengaluru – 560 076, India

8. Toll free number for reporting
1800 4190601

9. Date of text
5th July 2016