Summary of Product Characteristics

Cyclogest 400mg pessaries

1. Name of the medicinal product

CYCLOGEST 400mg

2. Qualitative and quantitative composition

Each pessary contains 400mg micronised Progesterone.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Off-white, torpedo-shaped pessaries.

4. Clinical particulars

4.1 Therapeutic indications

Cyclogest is indicated for the

1) Treatment of premenstrual syndrome, including premenstrual tension and depression.

2) Treatment of puerperal depression.

3) Luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women.

4.2 Posology and method of administration

For the treatment of premenstrual syndrome and puerperal depression:

200mg daily to 400mg twice a day, by vaginal or rectal insertion. For premenstrual syndrome commence treatment on day 14 of menstrual cycle and continue treatment until onset of menstruation. If symptoms are present at ovulation commence treatment on day 12.

For luteal phase support as part of an ART treatment:

400 mg administered vaginally twice a day starting at oocyte retrieval. The administration of Cyclogest should be continued for 38 days, if pregnancy has been confirmed.

Use in special populations: There is no experience with use of Cyclogest in patients with impaired liver or renal function.

Paediatric population: There is no relevant use of Cyclogest in the paediatric population.

Elderly: No clinical data have been collected in patients over age 65.

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.

- Severe hepatic dysfunction or disease

- Known missed abortion or ectopic pregnancy.

- Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.

4.4 Special warnings and precautions for use

Cyclogest is not indicated in threatened miscarriage. Treatment should be discontinued in the event of a missed miscarriage.

Cyclogest 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 progestins remains questionable. Therefore, in women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with Cyclogest may further increase the risk. In these women, the benefits of Cyclogest administration need to be weighed against the risks. It should be noted however, that pregnancy itself carries an increased risk of thrombo-embolic 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-progestin combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

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

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

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

Treatment of premenstrual syndrome and puerperal depression:

Use rectally if barrier methods of contraception are used.

Use rectally if patients suffer from vaginal infection (especially moniliasis) or recurrent cystitis or have recently given birth.

Use vaginally if patients suffer from colitis or faecal incontinence.

4.5 Interaction with other medicinal products and other forms of interaction

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 Cyclogest has not been assessed and is therefore not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

Cyclogest should not be used during pregnancy except as indicated during the first trimester of pregnancy for use as part of an assisted reproduction (ART) treatment 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.

Lactation

Progesterone is excreted in human milk and Cyclogest should not be used during breast-feeding

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

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), Not known (cannot be estimated from the available data)

SYSTEM ORGAN CLASS	**Common**	**Uncommon**	**Not known**
Nervous system disorder	Somnolence		
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort		Diarrhoea and flatulence may occur with rectal administration.
Skin and subcutaneous tissue disorders		Hypersensitivity reactions (e.g. rash, pruritus)	
Reproductive system and breast disorders	Breast pain		Menstruation may occur earlier than expected, or, more rarely, menstruation may be delayed.
General disorders and administration site conditions			Soreness, some leakage of the pessary base

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

SYSTEM ORGAN CLASS	**Common**	**Uncommon**
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		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

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 the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or via the Yellow Card app, which can be downloaded from the **Apple App Store**, or **Google Play Store**.

4.9 Overdose

There is a wide margin of safety with Cyclogest 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 Cyclogest 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 Cyclogest 400 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 Cmax after 10 days of multiple dosing was 18.4 [ng/mL] and Ctrough 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

There are no preclinical data of relevance to the prescriber which are additional to those already included in other sections of the SmPC.

6. Pharmaceutical particulars

6.1 List of excipients

Hard fat

6.2 Incompatibilities

None known

6.3 Shelf life

Shelf-life

4 years.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

The product may be supplied in strip packs contained in cartons:

Carton: *White backed folding box board printed on white.*

Strip pack: *Aluminium foil lacquer-laminated to 20µm polypropylene foil and coated on the reverse with polythene (20mg/m^2). The alternative is thermoplastic film and laminated PVC to 95µm and polyethylene to 27-33µm.*

Pack sizes: 5s, 12s, 15s

6.6 Special precautions for disposal and other handling

Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.

7. Applicant:

Alpha Phamacy And Stores [Nig] Ltd, 25, Salvation Road, Opebi Village, Lagos.

8. Manufacturer:

Fulton Medicinali S.P.A, Via Marconi 28/9-20044, Arese (Mi) Italy.