SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<invented name> 100 mg, Capsule, soft
<invented name> 200 mg, Capsule, soft

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains :

Progesterone ..... 100 mg

Progesterone ..... 200 mg

Excipient with known effect : Soya lecithin

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white Capsule, soft

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Disorders related to progesterone deficiencies in particular:
- Premenstrual syndrome
- Menstrual irregularities through dysovulation or anovulation
- Premenopause
- Replacement therapy of the menopause (in association with oestrogen therapy)

4.2. Posology and method of administration

Posology

In all the therapeutic indications, the recommended posology must be carefully respected.

For any indication, the posology will not exceed 200 mg per intake.

In progesterone deficiencies, the mean dose is of 200 to 300 mg of micronised progesterone per day.

In luteal insufficiencies (premenstrual syndrome, menstrual disorders and premenopause) the usual therapeutic regimen is of 200 to 300 mg per day:
- either 200 mg in a single intake at bedtime,
- or 300 mg in two intakes, 10 days per cycle, usually from the 17th to the 26th day included.

In hormone replacement therapy of the menopause, estrogen therapy alone is not recommended (risk of endometrial hyperplasia): progesterone must be added to the order of 200 mg per day:

- either in two intakes of 100 mg each,
- or in a single intake of 200 mg at bedtime, either 12 to 14 days per month, or the last two weeks of each therapeutic cycle.

Each treatment cycle will be followed by an interruption of all hormone therapy for around one week, during which it is usual to observe withdrawal bleeding.

Method of administration

This product is intended for oral use only.

The medicinal product should be taken away from mealtimes, preferably in the evening at bedtime. The second intake should be in the morning.

4.3. Contraindications

This medicinal product is contraindicated in cases of:

- Known allergy or hypersensitivity to progesterone or to any of the excipients listed in section 6.1,
- Severe hepatic dysfunction.
- Undiagnosed vaginal bleeding.
- Mammary or genital tract carcinoma, diagnosed or suspected.
- Thromboembolic disorders or thrombophlebitis, active or in the history
- Cerebral haemorrhage.
- Porphyria.

4.4. Special warnings and precautions for use

Warnings

– 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, or if unexplained, sudden or gradual, partial or complete loss of vision, proptosis or diplopia, papilloedema, retinal vascular lesions or migraine occur during therapy, the drug should be discontinued. In the latter case, appropriate diagnostic and therapeutic measures should be instituted. To prevent these latter complications, caution is to be taken in users more than 35 years old, in smokers and in those with risk factors of atherosclerosis.

– [INVENTED NAME] can be co-prescribed with an estrogen product as HRT. Epidemiological evidence suggests that the use of HRT is associated with an increased risk of developing deep vein thrombosis (DVT) or pulmonary embolism. The prescribing information for the co-prescribed estrogen product should be referred to for information about the risks of venous thromboembolism.

– There is suggestive evidence of a small increased risk of breast cancer with estrogen replacement therapy. It is not known whether concurrent progesterone influences the risk of cancer in post-menopausal women taking hormone replacement therapy. The prescribing information for the co-prescribed estrogen product should be referred to for information about the risks of breast cancer.

– More than half of spontaneous early abortions are due to genetic accidents. Moreover, infectious diseases and mechanical disorders may be responsible for early abortions. Administration of

progesterone would therefore only delay expulsion of a dead egg (or interruption of a non-evolving pregnancy).

– Use of progesterone must be reserved for cases of insufficient corpus luteum secretion.

– Treatment in the recommended conditions of use is not contraceptive.

Precautions

– Prior to taking hormone replacement therapy (and at regular intervals thereafter) each woman should be assessed. A personal and family medical history should be taken and physical examination should be guided by this and by the contraindications and warnings for this product.

– [INVENTED NAME] Capsules should not be taken with food and should be taken at bedtime. Concomitant food ingestion increases the bioavailability of [INVENTED NAME] Capsules.

– [INVENTED NAME] Capsules should be used cautiously in patients with conditions that might be aggravated by fluid retention (e.g. hypertension, cardiac disease, renal disease, epilepsy, migraine, asthma); in patients with a history of depression, diabetes, mild to moderate hepatic dysfunction, migraine or photosensitivity and in breast-feeding mothers.

– Clinical examination of the breasts and pelvic examination should be performed where clinically indicated rather than as a routine procedure. Women should be encouraged to participate in the national breast cancer screening programme (mammography) and the national cervical cancer screening programme (cervical cytology) as appropriate for their age. Breast awareness should also be encouraged and women advised to report any changes in their breasts to their doctor or nurse.

4.5. Interactions with other medicinal products and other forms of interaction

Drugs known to induce the hepatic CYP450-3A4 such as barbiturates, anti-epileptic agents (phenytoin, carbamazepine), rifampicin, phenylbutazone, spironolactone, griseofulvin, some antibiotics (ampicillins, tetracyclines) and also herbal products containing St. John's wort, [Hypericum perforatum] may increase the elimination of progesterone.
Ketokonazole and other inhibitors of CYP450-3A4 may increase bioavailability of progesterone.
Progesterone may interfere with the effects of bromocriptine and may raise the plasma concentration of ciclosporin.
Progesterone may affect the results of laboratory tests of hepatic and/or endocrine functions.
Progestogens may decrease glucose tolerance and thus, may increase insulin resistance or resistance to any other antidiabetic agents used in patients with diabetes mellitus.
Smoking may decrease progesterone bioavailability ; alcohol abuse may increase it.

4.6. Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicate no malformative nor feto/ neonatal toxicity of Progesterone.

Lactation

Detectable amounts of progesterone enter the breast milk. There is no indication for prescribing progesterone during lactation. However, progesterone intake during lactation does not seem to have deleterious effect on the baby growth.

Fertility
The product does not have deleterious effect on fertility.

4.7. Effects on ability to drive and use machines

It should be noted, particularly in persons driving and using machines, that there is a risk of drowsiness and/or dizzy spells associated with the use of this medicinal product.

4.8. Undesirable effects

Frequencies are defined as:

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
Not known	Frequency cannot be estimated from the available data

System Organ classes	*Common* ≥ 1 /100 - < 1/10	*Uncommon* ≥ 1/1.000 - < 1/100	*Rare* ≥ 1/10.000 - < 1/1.000	*Very rare* ≤ 1/10.000
Immune system disorders				urticaria
Metabolism and nutrition disorders		Fluid retention		
Nervous system disorders	headache	. drowsiness . fleeting dizziness		depression
Gastrointestinal disorders		gastro-intestinal disturbances	nausea	
Hepatobiliary disorders			jaundice	
Skin and subcutaneous tissue disorders		. rash . acne		Chloasma alopecia hirsutism
Reproductive system and breast disorders	. menstrual disturbances . amenorrhea ; vaginal bleeding	mastodynia		Changes in libido
General disorders and administration site condition				Pyrexia
Investigation			Change in weight	

			(increase or decrease)	

Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy (combining estrogens and progestogens) users than among non-users.

4.9. Overdose

Symptoms of overdosage may include somnolence, dizziness, euphoria or dysmenorrhea. 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
The active ingredient, progesterone, is chemically identical to the progesterone produced by the corpus luteum during the female ovarian cycle. It exerts many biological actions, mainly on target tissues previously sensitized by estrogens. Progesterone transforms proliferative endometrium into secretory state. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progesterone greatly reduces the oestrogen induced risk of endometrial hyperplasia in non-hysterectomised women.
In the mammary tissue, progesterone promotes the differentiation of ductal and lobular structures and antagonizes mesenchymal and epithelial effects of estradiol.
During pregnancy, progesterone increases endometrial receptivity for implantation of an embryo. Once the embryo has been implanted, progesterone acts to maintain the pregnancy. Progesterone also relaxes uterine smooth muscle.

5.2. Pharmacokinetic properties

Absorption
Micronised progesterone is absorbed in the digestive tract.
The increase in plasma progesterone starts one hour after ingestion and maximum progesterone levels are observed 1 to 3 hours after ingestion.
Pharmacokinetic studies conducted in volunteers show that after simultaneous ingestion of two capsules of PROGESTERONE EFFIK 100 mg, plasma progesterone reach a mean of 0.13 to 4.25 ng/ml after 1 hour, 11.75 ng/ml after 2 hours, 8.37 ng/ml after 4 hours, 2.00 ng/ml after 6 hours and 1.64 ng/ml after 8 hours.
In view of tissular retention time of the hormone, in order to obtain impregnation throughout the nycthemer, the posology should be divided into two intakes at 12-hours distance.

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

Biotransformation
In the plasma, the principle metabolites are 20α-hydroxy,Δ4α pregnanolone and 5α-dihydroprogesterone. Ninety-five percent of urinary elimination is in the form of glycuro-conjugated metabolites, mainly 3α, 5 β-pregnandiol. These plasma and urinary metabolites are identical to those found during physiological secretion of the ovarian corpus luteum.

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

Linearity/non-linearity
The pharmacokinetics of micronized progesterone is independent of the dose administered. Although there are considerable variations, the same individual retains the same pharmacokinetic characteristics at several months distance. This permits appropriate individual adaptation of the posology.

5.3. Preclinical safety data

Non-clinical safety data reveal no special hazards for humans as based on single dose toxicity and genotoxicity studies.
Animal studies on tumour promotion by progesterone showed conflicting results, with some indicating a tumour promoting effect and others a protective effect.
Reproductive toxicity studies showed adverse effects on male fertility, with suppression of spermatogenesis, as well as a potential for teratogenesis and prolongation of pregnancy at high doses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Safflower oil, refined (type II)
Capsule shell: gelatin, glycerol, titanium dioxide (E171), external manufacturing intermediates : traces of medium chain triglycerides and soya lecithin

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store above 30°C. Store in the original carton in order to protect from light.

6.5. Nature and contents of container

30 capsules in thermo-sealed blister (PVC/PVDC/Aluminium)
90 capsules in thermo-sealed blister (PVC/PVDC/Aluminium)
15 capsules in thermo-sealed blister (PVC/PVDC/Aluminium)
45 capsules in thermo-sealed blister (PVC/PVDC/Aluminium)

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

<{MM/YYYY}>

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS I