(a) (Arachis)

Utrogestan 200mg Capsules
Summary of Product Characteristics

1. NAME OF MEDICINAL PRODUCT

Utrogestan 200mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg micronised progesterone (INN). For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsules, soft
White

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Adjunctive use with estrogen in post-menopausal women with an intact uterus. (HRT)

4.2. Posology and method of administration

Posology

In women receiving estrogen replacement therapy there is an increased risk of endometrial cancer which can be countered by progesterone administration. The recommended dose is 200 mg daily at bedtime, for twelve days in the last half of each therapeutic cycle (beginning on day 15 of the cycle and ending on day 26). Withdrawal bleeding may occur in the following week.
Alternatively 100 mg can be given at bedtime from day 1 to day 25 of each therapeutic cycle, withdrawal bleeding being less with this treatment schedule.
Children: Not applicable.
Elderly: As for adults
Method of Administration: Oral. Utrogestan 200mg Capsules should not be taken with food

4.3. Contraindications

Known allergy or hypersensitivity to progesterone or to any of the excipients. The capsules contain arachis oil (peanut oil) and should never be used by patients allergic to peanuts. Severe hepatic dysfunction. Undiagnosed vaginal bleeding. Mammary or genital tract carcinoma. Thrombophlebitis. Thromboembolic disorders. Cerebral haemorrhage. Porphyria.

4.4. Special warning and precautions for use

Warnings:

Utrogestan 200mg Capsules are not a treatment for premature labour. Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.
Utrogestan 200mg Capsules are not suitable for use as a contraceptive.
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 and appropriate diagnostic and therapeutic measures instituted.
Utrogestan 200mg Capsules are intended to 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 coprescribed estrogen product should be referred to for information about the

risks of breast cancer.

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.

Utrogestan 200mg Capsules should not be taken with food and should be taken at bedtime. Concomitant food ingestion increases the bioavailability of Utrogestan 100mg Capsules.

Utrogestan 200mg 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. Interaction with other medicinal products and other forms of interaction

Utrogestan 200mg Capsules may interfere with the effects of bromocriptine and may raise the plasma concentration of cyclosporine. Utrogestan 200mg Capsules may affect the results of laboratory tests of hepatic and/or endocrine functions.

Metabolism of Utrogestan 200mg Capsules is accelerated by rifamycin an antibacterial agent.

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC_{50} <0.1 ìM 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. Pregnancy and lactation

Pregnancy

Utrogestan 200mg Capsules are not indicated during pregnancy. If pregnancy occurs during medication, Utrogestan 200mg Capsules should be withdrawn immediately.

Lactation

Detectable amounts of progesterone enter the breast milk. There is no indication for prescribing HRT during lactation.

4.7. Effects on ability to drive and use machines

Utrogestan 200mg Capsules may cause drowsiness and/or dizziness in a minority of patients; therefore caution is advised in drivers and users of machines. Taking the capsules at bedtime should reduce these effects during the day.

4.8. Undesirable effects

Somnolence or transient dizziness may occur 1 to 3 hours after intake of the drug. Bedtime dosing and reduction of the dose may reduce these effects.

Shortening of the cycle or breakthrough bleeding may occur. If this occurs, the dose of Utrogestan 200mg Capsules can be reduced and taken at bedtime from day 1 to day 26 of each therapeutic cycle.

Acne, urticaria, rashes, fluid retention, weight changes, gastro-intestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, menstrual disturbances; also chloasma, depression, 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.

4.9. Overdose

Symptoms of overdosage 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 (ATC code: G03D)

Progesterone is a natural progestogen, the main hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Utrogestan 200mg Capsules have all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular gestagenic, antiestrogenic, slightly antiandrogenic and antialdosterone effects.

5.2. Pharmacokinetic properties

Absorption

Micronised progesterone is absorbed by the digestive tract. Pharmacokinetic studies conducted in healthy volunteers have shown that after oral administration of 2 capsules (200mg), 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.

Although there were inter-individual variations, the individual pharmacokinetic characteristics were maintained over several months, indicating predictable responses to the drug.

Distribution

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

Elimination

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

Metabolism

Progesterone is metabolised primarily by the liver. The main plasma metabolites are 20 α hydroxy- Δ 4 α- prenolone and 5 α-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.

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
Soya lecithin
Gelatin
Glycerol
Titanium dioxide

6.2. Incompatibilities

None.

6.3. Shelf-life

3 years.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of container

The product is supplied in PVC/Aluminium blisters contained in cartons.

Pack size: 15 capsules per carton

6.6. Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Laboratoires BESINS INTERNATIONAL
3, rue du Bourg l'Abbé
75003
Paris
France

8. MARKETING AUTHORISATION NUMBER

PL 16468/0007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23rd February 2006

10. DATE OF REVISION OF THE TEXT

Supprimé : 5
Supprimé : 6
Supprimé : January
Supprimé : 5

(b) (Sunflower)

ANNEXE I

SUMMARY OF THE PRODUCT'S CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

UTROGESTAN 200 mg, oral or vaginal soft capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Progesterone……..200-mg

For one soft capsule

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral or vaginal soft capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral route

- Pre-menstrual syndrome,
- Menstrual irregularities due to ovulation disorders or anovulation,
- Benign mastopathy,
- Premenopause,
- Hormone replacement therapy for menopause (as an oestrogen complement).

Vaginal route

- Progesterone support during ovarian insufficiency or complete ovarian failure in women lacking ovarian function (oocyte donation).
- Luteal phase supplementation during in vitro fertilization (IVF) cycles,
- Luteal phase supplementation during spontaneous or induced cycles, in cases of hypofertility, in primary or secondary sterility and in particular due to dysovulation,
- Risk of miscarriage or prevention of repeated miscarriage due to luteal phase insufficiency up until the 12th week of pregnancy.
- For all other progesterone indications, the vaginal route represents an alternative to the oral route, in cases of:
- Adverse events due to progesterone (somnolence after absorption by the oral route).

4.2 Posology and method of administration

As in all therapeutic indications, it is important to strictly respect the recommended dose.

Regardless of the indication or the administration route (oral or vaginal), the dosage should not exceed 200-mg per dose.

Oral route

For progesterone insufficiency, the average dosage is 200 to 300-mg of micronized progesterone per day.

It is not recommended to take the medicine close to mealtimes; preferably, it should be taken in the evening before going to bed.

- **In cases of luteal insufficiency** (premenstrual syndrome, benign mastopathies, menstrual irregularities, premenopause) the usual therapeutic programme is 200 to 300-mg per day:
  - either 200-mg taken in one dose before bedtime,
  - or 300-mg taken in two doses, 10 days per cycle, normally from the 17th to the 26th day inclusive.
- **In replacement treatment for the menopause**, oestrogen therapy is not recommended on its own (risk of endometrial hyperplasia): progesterone should be added at a dosage of 200-mg per day:
  - 100-mg taken twice a day,
  - or in a single dose of 200-mg in the evening before going to bed, either for 12 to 14 days per month or during the last two weeks of each therapeutic sequence.

This treatment should be followed by an interruption of any substitutive treatment for roughly one week during which it is normal to experience a deprivation haemorrhage.

For these indications, the vaginal route should be used at the same dosage as the oral

route in the case of side effects due to the progesterone (drowsiness after oral absorption).

Vaginal route

Each capsule should be inserted as far as possible into the vagina.

- Progesterone substitution for ovarian insufficiency or complete deficiency in women without ovaries (oocyte donation).

The therapeutic programme (in complement to an appropriate oestrogenic treatment) is as follows:

- 100-mg of micronized progesterone per day on the 13th and 14th day of the transfer cycle then,
- 200-mg of micronized progesterone per day from the 15th to the 25th day of the cycle, spread over one or two daily doses, then,
- From the 26th day of the cycle and, in the case of the start of pregnancy, this dose can be increased to a maximum of 600-mg/day spread over three doses.

This posology can be followed until the 60th day, or at the latest, until the 12th week of pregnancy.

- **Supplementation of the luteal phase during IVF cycles:**

The recommended posology is 400 to 600-mg per day in two or three doses each day starting from the hCG injection and until the 12th week of pregnancy.

- **Supplementation of the luteal phase during spontaneous or induced cycles**, in cases of hypofertility or primary or secondary sterility, especially by dysovulation: the recommended posology is 200 to 300-mg per day in two doses starting from the 17th day of the cycle for 10 days. The treatment should be started again rapidly should menstruation not occur or pregnancy is diagnosed until the 12th week of pregnancy.
- **Risk of miscarriage or prevention of repeated miscarriages due to luteal insufficiency:** the recommended posology is 200 to 400-mg per day taken in two doses until the 12th week of pregnancy.

4.3 Contraindications

This medicine is contraindicated in the case of serious alterations to the hepatic function.

4.4 Special warnings and precautions for use

Special warnings:

- More than half of all early miscarriages are due to genetic accidents. Furthermore, infectious phenomena and mechanical problems can be responsible for miscarriages. Therefore, the only effect of the administration of progesterone would be to slow down the expulsion of a dead ovum (or the interruption of a non-evolutional pregnancy).
- The use of progesterone should only be reserved to cases where the secretion of the corpus luteum in insufficient.
- Under the recommended conditions of use, this treatment is not contraceptive.
- The use of UTROGESTAN 200-mg during a pregnancy is reserved to the first three months and for the vaginal route. UTROGESTAN 200-mg is not a treatment against the risk of premature birth.
- Cytolytic-type cases of hepatic attack and cases of gravidic cholestase have been reported on extremely rare occasions during the administration of micronized progesterone during 2nd and 3rd thirds of pregnancy.

4.5 Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6 Pregnancy and breast feeding

Numerous epidemiological studies on over one thousand patients have not shown any association between progesterone and foetal malformations.

4.7 Effects on ability to drive and use machines

Attention should be paid, especially for drivers of vehicles and those using machinery of the risks of drowsiness and/or dizziness attached to the use of this medicine when taking it by the oral route.

4.8 Undesirable effects

Oral route

- Drowsiness of transitory dizziness occurring 1 to 3 hours after ingestion of the product. In this case:
- Decrease the posology of each dose,
- Or modify the rhythm of the doses (i.e. for a dosage of 200-mg/day, take the 200-mg in the evening before bedtime in a single dose not close to mealtimes).
- Or adopt the vaginal route.
- Shortening of the menstrual cycle or intercurrent bleeding. Move the start of treatment to later on in the cycle (for example, start on the 19th day of the cycle in stead of the 17th).

In most cases, these effects indicate overdose.
Due to the presence of soya lecithin there is a risk of hypersensitive reactions occurring (anaphylactic shock, urticaria).

Vaginal route

- No local intolerance (burning, pruritus or fatty discharge) has been observed during the different clinical trials.
- No general side effect, in particular, drowsiness or dizziness has been reported during clinical studies at the recommended dosages.

4.9 Overdose

See part 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PROGESTERONE

(G03DA04: genito-urinary system and sexual hormones).

The properties of UTROGESTAN are comparable to those of natural progesterone, in particular, gestagen, anti-oestrogen, slightly anti-androgen and anti-aldosterone.

5.2 Pharmacokinetic properties

Oral route

Absorption
Micronized progesterone is absorbed by the digestive route.
Progesterone blood level rises during the first hour and the highest plasmatic levels are reached 1 to 3 hours after taking the medicine.
Pharmacokinetic studies carried out on volunteers have shown that after the simultaneous ingestion of two capsules of UTROGESTAN 100-mg, the progesterone blood level on average goes from 0.13-ng/ml to 4.25-ng/ml after one hour, 11.75-ng/ml after 2 hours, 8.37-ng/ml after 4 hours, 2-ng/ml after 6 hours and 1.64-ng/ml after 8 hours.
Given the tissue retention time of the hormone, it would appear necessary in order to obtain an impregnation the length of the nychthemeron, to spread the dosage over two doses roughly 12 hours apart.
There are noticeable individual variations, however, the same individual conserves the same pharmacokinetic characteristics for several months which leads to good individual adaptation to the posology.
Metabolism
In the plasma, the principle metabolites are 20α-hydroxy, _4-pregnanolone and 5α-dihydroprogesterone.
Urinary elimination is 95 % in the form of glycuroconjugated metabolites the principal of which is 3α-5β-pregnandiol. These plasmatic and urinary metabolites are identical to those found during the physiological secretion of the ovarian corpus luteum.

Vaginal route

Absorption
After vaginal insertion, the absorption of the progesterone by the vaginal mucous is rapid, as witnessed by the increase in the plasma progesterone levels one hour after its administration.
The maximum plasmatic concentration is attained 2 to 6 hours after insertion and is maintained at an average concentration over 24 hours of 9.7-ng/ml after administration

of 100-mg in the morning and evening. Therefore, this recommended average dosage brings about stable and physiological plasmatic concentrations of progesterone similar to those observed during the luteal phase of a normal ovulatory menstrual cycle. The low interpersonal variations in the levels of progesterone permit a precise forecast of the effect expected with a standard posology.
At doses above 200-mg per day, the concentrations of progesterone obtained are comparable to those described during the first three months of pregnancy.
Metabolism
The concentration of 5β-pregnanolone is not augmented in the plasma.
Urinary elimination is mainly in the form of 3α, 5β-pregnandiol as is witnessed by the progressive increase in its concentration (until it attains the maximum concentration of 142-ng/ml by the 6th hour).

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sunflower oil, soya lecithin
Capsule shell: gelatine, glycerine and titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

There are no special precautions for storage.

6.5 Nature and contents of container

14, 15, 30 or 60 capsules in blister packs (PVC/aluminium)

6.6 Special precautions for disposal and other handling

No particular requirements.

7. MARKETING AUTHORIZATION HOLDER

LABORATOIRES BESINS INTERNATIONAL
3, rue du Bourg l'Abbé
75003 PARIS – FRANCE

8. MARKETING AUTHORIZATION NUMBERS

- 361 988-1: 14 capsules in a blister pack (PVC/aluminium).
- 348 399-6: 15 capsules in a blister pack (PVC/aluminium).
- 348 400-4: 30 capsules in a blister pack (PVC/aluminium).
- 348 401-0: 60 capsules in a blister pack (PVC/aluminium).

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

(To be completed by the authorization holder)

10. DATE OF REVISION OF THE TEXT

(To be completed by the authorization holder)

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

CONDITIONS FOR PRESCRIPTION AND ISSUE

List I