Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Utrogestan 100 mg capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg micronized progesterone as the active ingredient.
Excipients with known effect: Contains 1.0 mg Soybean lecithin.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule (capsules)
Round and slightly yellow soft capsules, containing whitish oily suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Utrogestan is indicated for adjunctive use with estrogen in post-menopausal women with an intact uterus, as hormone replacement therapy (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 12 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.

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

Older people
As for adults

Method of Administration:
Oral
Utrogestan 100 mg Capsules should not be taken with food and should be taken at bedtime.
Concomitant food ingestion increases the bioavailability of micronized progesterone.

4.3 Contraindications

When used in conjunction with estrogens, Utrogestan should not be used in patients with any of the following conditions

- Known hypersensitivity to the active substances, soya lecithin, peanut or to any of the excipients listed in section 6.1
- Known, past or suspected breast cancer
- Known or suspected estrogen-dependent malignant tumours (*e.g.* genital tract carcinoma)
- Undiagnosed genital bleeding
- Previous or current thromboembolism disorders (*e.g.* deep venous thrombosis, pulmonary embolism) or thrombophlebitis
- Known thrombophilic disorders
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal

- Porphyria
- Cerebral haemorrhage
- Breast feeding (see section 4.6)

4.4 Special warnings and precautions for use

Warnings:

- For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.
- Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Utrogestan 100 mg Capsules are not suitable:

- In confirmed pregnancy (see section 4.6)
- in the treatment of premature labour, or
- as a contraceptive.

Precautions

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, *e.g.* mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Utrogestan 100 mg Capsules, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours, *e.g.* 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (*e.g.* liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis
- Depression
- Photosensitivity

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication is discovered and in the following situations;

- Jaundice or deterioration in liver function

- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy
- Sudden or gradual, partial or complete loss of vision
- Proptosis or diplopia
- Papilloedema
- Retinal vascular lesions

Endometrial Hyperplasia and carcinoma

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.
The addition of progesterone for at least 12 days per month/28 day cycle or continuous combined estrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT.

Break-through bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding persists, a lower dose of Utrogestan for 25 days per cycle could be considered (see section 4.2).

If break-through bleeding and spotting appears after some time on therapy, or continues after treatment has been discontinued, this should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast Cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined estrogen-progestogen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT.
Combined oestrogen-progestagen therapy

- The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestagen for HRT that becomes apparent after about 3 years (see Section 4.8).

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

HRT, especially estrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer
Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see Section 4.8).

Venous thromboembolism

HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), *i.e.* deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).

Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

Generally recognised risk factors for VTE include, use of estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).
If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (*e.g.* antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.
Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (eg, painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)
There is no evidence from randomised controlled clinical trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestogen or estrogen-only HRT.
Combined estrogen-progestogen therapy

- The relative risk of CAD during use of combined estrogen+progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic stroke

Combined estrogen-progestogen and estrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8)

Other conditions

HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

Utrogestan 100 mg Capsules contains soybean lecithin and may cause hypersensitivity reactions (urticarial and anaphylactic shock in hypersensitive patients). As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Utrogestan 100mg Capsules.

4.5 Interaction with other medicinal products and other forms of interactions

Enzyme inducers
Drugs known to induce the hepatic CYP450-3A4 such as barbiturates, anti-epileptic agents (phenytoin, carbamazepine), rifampicin, phenylbutazone, bromcriptine, spironolactone, griseofulvin, some antibiotics (ampicillins, tetracyclines) and also herbal products containing St. John's wort, (*Hypericum perforatum*) may increase metabolism and the elimination of progesterone.

Enzyme inhibitors
Ketoconazole and other inhibitors of CYP450-3A4 such as ritonavir and nelfinavir may increase bioavailability of progesterone. The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 <0.1 µM).

Immunosuppressants
Progesterone may raise the plasma concentration of ciclosporin.

Antisteroidal drugs

Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic enzyme-inducing effect.

Anticoagulants
Progesterone may enhance or reduce the anticoagulant effect of coumarins.
Progesterone antagonises the anticoagulant effect of phenindione.

Diabetic medications
An adjustment in anti-diabetic dosage may be required for women being treated concomitantly with progesterone.

Emergency contraceptives
The concomitant use of ulipristal acetate with progesterone may result in reduced efficacy of progesterone.

Diazepam
Progesterone may increase the plasma concentration of diazepam.

Tizanidine
Progesterone may increase the plasma concentration of tizanidine.

Terbinafine
There have been occasional reports of breakthrough bleeding when terbinafine is used concomitantly with progesterone.

Laboratory tests
Progesterone may affect the results of laboratory tests of hepatic and/or endocrine functions.

4.6 Fertility, pregnancy and lactation

Pregnancy
If pregnancy occurs during medication, Utrogestan 100 mg Capsules should be withdrawn immediately.
Clinically, data on a large number of exposed pregnancies indicate no adverse effects of progesterone on the foetus. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens+progesterone indicate no teratogenic or foetotoxic effect.

Prescription of high-dose oral progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.

Breast-feeding
Utrogestan 100 mg Capsules is not indicated during breast feeding (see section 4.3). Progesterone is distributed into breast milk.

Fertility
Not relevant

4.7 Effects on ability to drive and use machines

This medicine may cause drowsiness or dizziness therefore care should be taken when driving or using machines

4.8 Undesirable effects

a. Summary of the safety profile
The reporting rate of adverse drug reactions with Utrogestan Oral and Vaginal formulations was calculated as 1.43/1,000 patient year's corresponding to approximately 1.5 spontaneously reported cases in every 1000 patients exposed to Utrogestan (Periodic Benefit Risk Evaluation Report 01 January 2012 – 31 December 2017).

b. Tabulated list of adverse reactions

Clinical trial data
The table below lists adverse experiences which were reported in > 10% of patients (regardless of relationship to treatment) who received cyclic micronized Progesterone capsules, 200 mg daily (12 days per calendar month cycle) with daily 0.625 mg

conjugated estrogen, in a multicenter, randomised, double-blind, placebo-controlled clinical trial (Postmenopausal Estrogen and Progestin Interventions (PEPI) Trial) in 875 postmenopausal women.

Adverse experiences (>10%) reported in an 875 patient placebo-controlled trial in postmenopausal women over a 3-year period				
System Organ Class	Preferred Term	Micronized progesterone capsules 200 mg with conjugated estrogens 0.625 mg (N=178)	Conjugated estrogens 0.625 mg (only) (N=175)	Placebo (N=174)
Gastrointestinal disorders	Abdominal bloating	12	10	5
	Abdominal pain	10	13	10
Nervous system disorders	Headache	31	30	27
	Dizziness	15	5	9
Psychiatric disorders	Depression	19	18	12
Reproductive system and breast disorders	Breast tenderness	27	16	6
	Hot flushes	11	14	35
	Vaginal discharge	10	10	3
Miscellaneous	Joint pain	20	22	29
	Urinary problems	11	10	9

Post-Marketing experience
The information given below is based on extensive post marketing experience, primarily from oral administration of progesterone.

Adverse effects have been ranked under headings of frequency using the following convention: 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); frequency not known (cannot be estimated from the available data).

System organ class	Frequency Not known (cannot be estimated from the available data)
Gastrointestinal disorders	Abdominal pain Nausea
General disorders and administration site conditions	Fatigue
Nervous system disorders	Headache Somnolence Dizziness
Reproductive system and breast disorders	Vaginal haemorrhage
Skin and subcutaneous tissue disorders	Pruritus

c. Description of selected adverse reactions
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.

The following risks apply in relation to systemic estrogen/progestogen treatment:

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of estrogen-progestogen combinations.

- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period*2	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
estrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined estrogen-progestogen			
50-65	9-12	1.7	6 (5-7)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately. *2 *Taken from baseline incidence rates in developed countries*			

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*3
CEE+MPA oestrogen & progestagen‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)
‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users. *3 *WHI study in women with no uterus, which did not show an increase in risk of breast cancer*			

Endometrial cancer risk

Postmenopausal women with a uterus.
The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.
In women with a uterus, use of estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of estrogen-only use and estrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding progesterone to estrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study (MWS) the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Use of estrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*4			
50-59	7	1.2 (0.6 – 2.4)	1 (-3 – 10)
Oral combined estrogen-progestogen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 – 13)
*4 *Study in women with no uterus*			

Risk of coronary artery disease

- The risk of coronary artery disease is slightly increased in users of combined estrogen-progestogen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of estrogen-only and estrogen + progestogen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke*5 over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users
50-59	8	1.3 (1.1 – 1.6)	3 (1 – 5)
5**no differentiation was made between ischaemic and haemorrhagic stroke.*			

The following adverse reactions have also been reported in association with systemic oestrogen/ progestogen treatment:

- Rash
- Urticaria
- Chloasma/ melasma
- Pyrexia

- Insomnia
- Alopecia
- Irregular menstruation
- Amenorrhoea
- Breast pain/ mastodynia
- Fluid retention/ oedema
- Weight changes
- Changes in libido
- Depression
- Gall bladder disease
- Probable dementia over the age of 65 (see section 4.4)
- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura

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 HPRA Pharmacovigilance; Website: www.hpra.ie .

4.9 Overdose

Symptoms
High doses of progesterone may cause drowsiness, dizziness, somnolence or fatigue.

Treatment
Treatment of overdosage consists of discontinuation of Utrogestan together with institution of appropriate symptomatic and supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system;
Progestogens; Pregnen-(4) derivatives
ATC Code: G03DA04

Mechanism of action
Progesterone is a natural progestogen, in 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 100mg Capsules have all the properties of endogenous progesterone, in particular gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects.

Clinical efficacy and safety
As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of progesterone greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

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.

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).

Biotransformation
Progesterone is metabolized 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.

Linearity/non-linearity
The pharmacokinetics of micronized progesterone is independent of the dose administered. Although there were some inter-individuals variations, the same individual pharmacokinetic characteristics were maintained over several months permitting appropriate individual adaptation of the posology and indicating predictable responses to the drug.

Older people
As per adults above

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sunflower Oil, refined
Soybean Lecithin
Gelatin
Glycerol (E422)
Titanium Dioxide (E171)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Utrogestan 100 mg Capsules, Soft are packed in PVC/Aluminium blisters of 10 capsules each. It is supplied in packs of three blisters containing 30 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoires Besins International
3, rue du Bourg l'Abbe
75003 Paris
France

8 MARKETING AUTHORISATION NUMBER

PA1054/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 February 1988

Date of last renewal: 09 February 2008

10 DATE OF REVISION OF THE TEXT

June 2022