

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Progesterone 100 mg, Capsule, soft
Gepretix 100 mg, Capsule soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Progesterone 100 mg

Excipient(s) with known effect: soya bean lecithin

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

Progesterone 100 mg: Ovoid soft gelatine capsules off-white coloured approx. 12 mm long and approx. 8 mm wide.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Progesterone 100 mg is indicated for adjunctive use with an oestrogen in post-menopausal women with an intact uterus, as hormone replacement therapy (HRT).

4.2 Posology and method of administration

Posology

In women receiving oestrogen replacement therapy there is an increased risk of endometrial cancer which can be countered by progesterone administration.

The recommended dose is 200mg 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 100mg 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 Progesterone in the paediatric population.

Older people

As for adults

Method of administration

This product is intended for oral use only.

Progesterone 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 oestrogens, Progesterone should not be used in patients with any of the following conditions:

- Known hypersensitivity to the active substances, soybean lecithin, peanut or to any of the excipients listed in section 6.1
- Known, past or suspected breast cancer
- Known or suspected oestrogen-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.

Progesterone 100 mg soft 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 reinstating 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 Progesterone 100 mg soft capsules, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen 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 oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen 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 oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.oestrogen

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

If breakthrough bleeding or spotting appears some time on therapy, or continues after treatment has been discontinued, the reason 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 oestrogen-progestogen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen 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 oestrogen-progestogen 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 oestrogen-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 oestrogen-only or combined oestrogen-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 oestrogens, 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 (*e.g.* painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT.

Combined oestrogen-progestogen therapy

- The relative risk of CAD during use of combined oestrogen+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 oestrogen-progestogen and oestrogen-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 oestrogen-only HRT after the age of 65.

Progesterone 100 mg soft capsules contain 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 Progesterone 100 mg soft capsules

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme inducers

Drugs known to induce the hepatic CYP450-3A4 such as barbiturates, anti-epileptic agents (phenytoin, carbamazepine), rifampicin, phenylbutazone, bromocriptine, 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 is expected to 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, Progesterone 100mg soft 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 oestrogens + progesterone indicate no teratogenic or foetotoxic effect.

Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.

Breast-feeding

Progesterone 100 mg soft 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 progesterone 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 progesterone.

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 oestrogen, in a multicenter, randomised, double-blind, placebo-controlled clinical trial (Postmenopausal Oestrogen 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 oestrogens 0.625 mg (N=178)	Conjugated oestrogens 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 ($\geq 1/10$); common ($\geq 1/100$; $< 1/10$); uncommon ($\geq 1/1,000$; $< 1/100$); rare ($\geq 1/10,000$; $< 1/1,000$); 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 oestrogen/progestogen treatment:

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-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 oestrogen-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)
Oestrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined oestrogen-progestogen			
50-65	9-12	1.7	6 (5-7)
<p>#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</p>			

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 & progestogen‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)
<p>‡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</p>			

Endometrial cancer risk

Postmenopausal women with an uterus.

The endometrial cancer risk is about 5 in every 1000 women with an uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen 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 oestrogen-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 oestrogen-only and combined oestrogen-progestogen 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 (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 oestrogen-only*4			
50-59	7	1.2 (0.6 – 2.4)	1 (-3 – 10)
Oral combined oestrogen-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 oestrogen-progestogen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

The use of oestrogen-only and oestrogen + progestagen 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 that have been reported in association with systemic oestrogen / progestagen 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 the website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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

Treatment

Treatment of overdosage consists of discontinuation of Progesterone 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, the main hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Progesterone 100mg soft capsules have all the properties of endogenous progesterone, in particular gestagenic, antioestrogenic, slightly anti-androgenic and antialdosterone effects.

Clinical efficacy and safety

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.

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 C_{max} 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 glycoconjugated metabolites, mainly 3 α , 5 β -pregnanediol (pregnandiol).

Biotransformation

Progesterone is metabolised primarily by the liver. The main plasma metabolites are 20 α -hydroxy, Δ 4 pregnenolone 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-individual 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

Non-clinical 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

Grape seed oil

Soya bean lecithin

Capsule shell:

- Gelatin
- Glycerol
- Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

15 capsules in thermo-sealed blister (PVC/PE/PVDC/Aluminium or PVC/PVDC/Aluminium)

30 capsules in thermo-sealed blister (PVC/PE/PVDC/Aluminium or PVC/PVDC/Aluminium)

45 capsules in thermo-sealed blister (PVC/PE/PVDC/Aluminium or PVC/PVDC/Aluminium)

60 capsules in thermo-sealed blister (PVC/PE/PVDC/Aluminium or PVC/PVDC/Aluminium)

90 capsules in thermo-sealed blister (PVC/PE/PVDC/Aluminium or PVC/PVDC/Aluminium)

Not all pack sizes may be marketed.

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

EXELTIS HEALTHCARE, S.L.

Avenida Miralcampo, 7 - Polígono Industrial Miralcampo,

19200 Azuqueca de Henares -Guadalajara, Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 44081/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/03/2023

10 DATE OF REVISION OF THE TEXT

30/09/2024