

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NOGEST 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is nomegestrol acetate, 5mg.

Excipient with known effect: each tablet contains 120.99 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, oblong tablet with a scoreline.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In pre-menopausal women: treatment of menstrual cycle disturbances associated with insufficient or absent progesterone secretion, particularly in cases of:

- menstrual cycle abnormalities: oligomenorrhoea, polymenorrhoea, spaniomenorrhoea, amenorrhoea (following aetiological evaluation).
- functional genital bleeding: metrorrhagia, menorrhagia, including bleeding associated with the presence of uterine leiomyomas.
- functional symptoms before or during menstruation: primary dysmenorrhoea, premenstrual syndrome, cyclic mastodynia.

In postmenopausal women: as Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in combination with oestrogens in non-hysterectomised women with at least 6 months since last menses.

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

The usual dosage is one tablet per day (5 mg/day).

- In pre-menopausal women: the usual dosage consists of a 10-day course of treatment, 1 tablet per day from days 15 to 24 of the menstrual cycle inclusive.
- In post-menopausal women or amenorrhoea: the Nogest dosage depends on the mode of Hormone Replacement Therapy. In cyclic and continuous sequential regimens, Nogest is prescribed for 10 to 14 days per cycle.

Dosage and duration of treatment may be adjusted in all cases, depending on the severity of symptoms or clinical response.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used.

There is no relevant use of Nogest in children.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Porphyria.

4.4 Special warnings and precautions for use

- 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 favorable than in older women.
- Nogest is not suitable for use as a contraceptive.

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.
- Prior to commencing treatment in certain indications, such as uterine bleeding, amenorrhoea or dysmenorrhoea, a previous aetiological assessment should be made to ensure the functional nature of the condition. A clinical investigation, possibly supplemented by additional tests, is particularly recommended to ensure the absence of uterine cancer (cervix, endometrium) and breast cancer.

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 Nogest, 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

Reasons for immediate withdrawal of the 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

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 a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.
- Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after 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-progestagen and possibly also oestrogen-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 oestrogen-progestagen for HRT that becomes apparent after about 3 years (see Section 4.8).

Oestrogen-only therapy

- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestagen combinations (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-progestagen 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. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer 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 immobilization 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 mobilized.
- 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, dyspnea).

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-progestagen or oestrogen-only HRT:

Combined oestrogen-progestagen therapy

The relative risk of CAD during use of combined oestrogen+progestagen 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+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only

Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

- Combined oestrogen-progestagen 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

- Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- 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.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (*Hypericum Perforatum*) may induce the metabolism of oestrogens and progestagens.

Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Fertility, pregnancy and lactation

Pregnancy

Nogest is not indicated during pregnancy. If pregnancy occurs during medication with Nogest treatment should be withdrawn immediately.

Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of nomegestrol acetate on the foetus. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens + progestagens indicate no teratogenic or foetotoxic effect.

Breastfeeding

Small amounts of steroids are excreted into breast milk. Nogest is therefore not recommended for use during breast-feeding.

Fertility

The experience on male and female fertility is limited.

4.7 Effects on ability to drive and use machines

Nogest has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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 national reporting system listed in [Appendix V](#).

Tabulated summary of adverse reactions

Organ system class	Common ADRs >1/100, <1/10	Uncommon ADRs >1/1 000, <1/100	Very rare ADRs <1/10 000
Gastrointestinal disorders			Gastrointestinal disturbances
Skin and subcutaneous tissues disorders			Allergic cutaneous eruption
Neurological disorders	Headaches		
Vascular disorders			Venous thromboembolic events
Reproductive system and breast disorders		Changes in menstruation, amenorrhoea, breakthrough bleeding.	

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:

- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).

Description of selected adverse reactions observed in the context of an HRT

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen 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-progestagen 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*	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-progestagen			
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.			
the TC we finally decided to re-include the figures of table 2 of the Million Women study.			

*Taken from baseline incidence rates in developed countries

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

Age range (yrs)	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)*
CEE+MPAestrogen&progestagen‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

*WHI study in women with no uterus, which did not show an increase in risk of breast cancer

‡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.

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 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 a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study 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

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

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 and 95% CI	Additional cases per 1000 HRT users
Oral oestrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 – 13)

*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-progestagen 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* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1-1.6)	3 (1-5)

*no differentiation was made between ischaemic and haemorrhagic stroke

4.9 Overdose

No case of harmful effects has been reported during clinical trials when the highest dose administered to patients over several weeks was up to 10 times the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Group of hormones / Progestogens, ATC code: G03DB04.
Progestogen derived from 19-nor-progesterone.

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Mechanism of action

Administration of 5 mg nomegestrol acetate per day, from days 5 to 24, suppresses the gonadotropin ovulation peak, decreases the level of circulating oestrogens and blocks the release of progesterone.

Pharmacodynamic effects

True progestogen, compensating for the lack of progesterone. Affinity of nomegestrol acetate for the progesterone receptor is 2.5 times greater than that of the natural hormone.

Nomegestrol acetate is devoid of androgenic, anabolic, oestrogenic and adrenocortical activity. No interference has been observed with carbohydrate metabolism or the fluid and electrolyte balance. Nomegestrol acetate does not affect bromsulphalein clearance.

Clinical efficacy and safety

All clinical and biological studies reveal that Nogest has good, general and digestive tolerability without any concomitant adverse hormonal, vascular, hepatic or metabolic effects.

5.2 Pharmacokinetic properties

Pharmacokinetic studies, conducted after single-dose administration, indicate that:

Absorption

Digestive absorption is rapid, with peak plasma levels being reached 2 hours after taking the product.

Distribution

Nomegestrol acetate has a high plasma protein binding rate of $97.7 \pm 0.1\%$, which is similar to that of progesterone (97.2 to 97.6%). Nomegestrol acetate is not bound to either SHBG or CBG.

Biotransformation

The major metabolites are hydroxylated derivatives; they are partially conjugated (glucuronide and sulphate conjugates), with elimination taking place mainly via the intestinal route and partially via the urinary route.

Elimination

The elimination half-life is about 40 hours.

Good availability of nomegestrol acetate after oral administration, together with its long half-life, allows single daily administration.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Microcrystalline cellulose,
Silica colloidal,
Glyceryl palmitostearate.

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

Blister: PVC/aluminium.

Pack sizes: 1 x 10 tablets,
3 x 10 tablets,
3 x 14 tablets,
6 x 10 tablets,
6 x 14 tablets,
9 x 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]