

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Noviana 0.5 mg/0.1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Estradiol 0.5 mg (as estradiol hemihydrate) and norethisterone acetate 0.1 mg.

Excipient: Each film-coated tablet contains lactose monohydrate 37.5 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex tablets with a diameter of 6 mm. The tablets are engraved with “NOVO 291” on one side and the “APIS” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in women more than one year after menopause.

The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Noviana is a continuous combined hormone replacement therapy intended for use in women with an intact uterus. One tablet should be taken orally once a day without interruption, preferably at the same time every day.

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.

A switch to a higher dose product, e.g. Activelle 1 mg/0.5 mg tablets, should be considered if the response after three months is insufficient for satisfactory symptom relief.

In women with amenorrhea and not taking HRT or women transferring from another continuous combined HRT product, treatment with Noviana may be started on any convenient day. In women transferring from sequential HRT regimens, treatment should start right after their withdrawal bleeding has ended.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next twelve hours. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known, past 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 previous 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
- Known hypersensitivity to the active substances or to any of the excipients
- 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 favourable than in older women.

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 and 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 Noviana 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 therapy

Therapy should be discontinued in case a contra-indication (see section 4.3) 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 more than 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.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting continues after the first months of treatment, appears after some time during 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.

The randomised placebo-controlled trial and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT (see section 4.8).

The excess risk becomes apparent after about 3 years of use but returns to baseline within a few (at most 5) years after stopping treatment.

HRT, specially 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- to 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 to 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 a 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-progestagen or oestrogen-only HRT.

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.

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

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

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.

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, and ceruloplasmin).

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.

Noviana contains lactose monohydrate. Patients with any of the following rare hereditary diseases should not take this medicine: galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

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.

Drugs that inhibit the activity of hepatic microsomal drug metabolising enzymes e.g. ketoconazole, may increase circulating levels of the active substances in Noviana.

Concomitant administration of cyclosporine and Noviana may cause increased blood levels of cyclosporine, creatinine and transaminases due to decreased metabolism of cyclosporine in the liver.

4.6 Fertility, pregnancy and lactation

Pregnancy

Noviana is not indicated during pregnancy.
If pregnancy occurs during medication with Noviana, treatment should be withdrawn immediately.
Clinically, data on a limited number of exposed pregnancies indicate adverse effects of norethisterone on the foetus. At doses higher than normally used in OC and HRT, formulations masculinisation of female foetuses was observed.
The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestagens indicate no teratogenic or foetotoxic effect.

Lactation

Noviana is not indicated during lactation

4.7 Effects on ability to drive and use machines

Noviana has no known effect on the ability to drive and use machines.

4.8 Undesirable effects

Clinical experience

The most frequently reported adverse event in the clinical trial with Noviana was vaginal bleeding. 11% of women at month 1, 15% of women at month 4 and 11 % of women at the end of the 6 month trial reported bleeding or spotting. All adverse reactions observed with a higher frequency in patients treated with Noviana compared to placebo and which on an overall judgement are possible related to treatment are presented below.

System organ class	Very common ≥ 1/10	Common ≥ 1/100; < 1/10	Uncommon ≥ 1/1,000; < 1/100	Rare ≥ 1/10,000; < 1/1,000
Infections and infestations		Vulvovaginal mycotic infection, see also Reproductive system and breast disorders		
Immune system disorders			Hypersensitivity, see also Skin and subcutaneous tissue disorders	
Metabolism and nutrition disorders			Fluid retention, see also General disorders and administration site conditions	
Psychiatric disorders			Depression or depression aggravated Nervousness	
Nervous system disorders		Headache	Migraine Dizziness	
Gastrointestinal disorders		Abdominal pain Nausea	Abdominal distension Dyspepsia	
Skin and subcutaneous tissue disorders			Pruritus or Urticaria Alopecia	

			Acne	
Musculoskeletal and connective tissue disorders		Back pain Neck pain Pain in extremity	Leg cramps	
Reproductive system and breast disorders	Vaginal haemorrhage	Endometrial thickening Vulvovaginal mycotic infection	Breast pain Breast discomfort	
General disorders and administration site conditions			Oedema peripheral	

Post-marketing experience

In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgement considered possibly related to Activelle 1 mg/0.5 mg treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (< 1/10,000, not known (cannot be estimated from the available data)). Post-marketing experience is subject to underreporting especially with regard to trivial and well-known adverse drug reactions. The presented frequencies should be interpreted in that light:

- Neoplasms benign and malignant (including cysts and polyps): Endometrial cancer
- Immune system disorders: Generalised hypersensitivity reactions (e.g. anaphylactic reaction/shock)
- Psychiatric disorders: Insomnia, anxiety, libido decreased, libido increased
- Nervous system disorders: Dizziness, stroke
- Eye disorders: Visual disturbances
- Cardiac disorders: Myocardial infarction
- Vascular disorders: Hypertension aggravated
- Gastrointestinal disorders: Dyspepsia, vomiting
- Hepatobiliary disorders: Gallbladder disease, cholelithiasis, cholelithiasis aggravated, cholelithiasis reoccurrence
- Skin and subcutaneous tissue disorder: Seborrhoea, rash, angioneurotic oedema
- Reproductive system and breast disorders: Hyperplasia endometrial, vulvovaginal pruritus
- Investigations: Weight decreased, blood pressure increased

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

- Skin and subcutaneous disorders: Alopecia, chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (For further information, see section 4.4)

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 below.

Million Women Study – Estimated additional risk of breast cancer after 5 years’ use

Age range (years)	Additional cases per 1,000 never-users of HRT over a 5-year period*	Risk ratio and 95% CI**	Additional cases per 1,000 HRT users over 5 years use (95% CI)
Oestrogen-only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined oestrogen-progestagen			
50-65	9-12	1.7	6 (5-7)

* Taken from baseline incidence rates in developed countries.
** Overall risk ratio. The risk ration 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 proportionally.

US WHI Studies – Additional risk of breast cancer after 5 years’ use

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 HRT users over 5 years (95% CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7-1.0)	-4 (-6-0)*
CEE+MPA oestrogen-progestagen**			
50-79	14	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

The endometrial cancer risk is about 5 in every 1,000 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 epidemiological studies varied from between 5 and 55 extra cases diagnosed in every 1,000 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 5 years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer risk

Long-term use of oestrogen-only and combined oestrogen-progestogen 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 2,500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3- to 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 HRT (see section 4.4). Results of the WHI studies are presented below.

WHI Studies – Additional risk of VTE over 5 years’ use

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 HRT users (95% CI)
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 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 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 HRT users (95% CI)
50-59	8	1.3 (1.1-1.6)	3 (1-5)

* No differentiation was made between ischaemic and haemorrhagic stroke

4.9 Overdose

Overdose may be manifested by nausea and vomiting. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestagens and oestrogens, fixed combinations, ATC code: G03FA01.

Estradiol: The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Norethisterone acetate: Synthetic progestagen with actions similar to those of progesterone, a natural female sex hormone. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen reduces, but does not completely eliminate, the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Relief of menopausal symptoms is achieved during the first few weeks of treatment. By Week 3, the decrease in mean number of moderate to severe hot flushes for the 0.5 mg estradiol treatment group was statistically significant (p≤0.001) when compared to the placebo group. This reduction remained until the conclusion of the study at week 24.

Noviana is a continuous combined HRT product containing 17β-estradiol and norethisterone acetate with the intent of avoiding the regular withdrawal bleeding associated with cyclic or sequential HRT. Amenorrhoea (no bleeding or spotting) was seen in 89% of the women in month 6 of treatment. Bleeding and/or spotting appeared in 11 to 15% of the women during the first 6 months of treatment.

5.2 Pharmacokinetic properties

Following oral administration of Noviana, 17β -estradiol is absorbed from the gastrointestinal tract, undergoes a first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration within 5-8 hours. After administration of 2 Noviana tablets, the average peak plasma concentration was 24 pg/ml (CV 38 %). The half-life of 17β -estradiol is about 15 hours. It circulates bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound. Metabolism of 17β -estradiol, occurs mainly in the liver and gut but also in target organs, and involves the formation of less active or inactive metabolites, including oestrone, catecholoestrogens and several oestrogen sulphates and glucuronides. Conjugated oestrogens are excreted by the bile, where they are hydrolysed and reabsorbed (enterohepatic circulation), and mainly in urine in biologically inactive form.

After oral administration of an Noviana tablet, norethisterone acetate is rapidly absorbed and transformed to norethisterone (NET). It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 2.4 ng/ml CV 41% (after administration of 2 Noviana tablets) within 0.5 - 1.5 hours. The terminal half-life of NET is about 9-11 hours. NET binds to SHBG (36%) and to albumin (61%). The most important metabolites are isomers of 5α -dihydro-NET and of tetrahydro-NET, which are excreted mainly in the urine as sulphate or glucuronide conjugates.

The pharmacokinetics of estradiol is not influenced by norethisterone acetate.

The pharmacokinetic properties in the elderly have not been studied.

5.3 Preclinical safety data

The acute toxicity of estrogens is low. Due to the large differences between animal species and between animals and humans, preclinical results are of limited value for predicting the effect on humans.

Animal studies have shown embryo-lethal effects of estradiol or estradiol valerate even at relatively low doses; malformations of the urogenital tract and feminization of male foetuses were observed.

Like other progestagens, norethisterone causes virilization of female fetuses in rats and monkeys. At high doses of norethisterone embryo-lethal effects were observed.

Non-clinical data based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential reveal no special hazard for humans apart from those already discussed in other sections of the summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Maize starch
Hydroxypropylcellulose
Talc
Magnesium stearate

Film-coating:

Hypromellose
Triacetin
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate. Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

1 x 28 tablets or 3 x 28 tablets in calendar dial packs.

The calendar dial pack with 28 tablets consists of the following 3 parts:

- The base made of coloured non-transparent polypropylene
- The ring-shaped lid made of transparent polystyrene
- The centre-dial made of coloured non-transparent polystyrene

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8 MARKETING AUTHORISATION NUMBER

PA 218/54/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 February 2010

10 DATE OF REVISION OF THE TEXT

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