SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Novofem film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One red film-coated tablet contains:
Estradiol 1 mg (as estradiol hemihydrate).

One white film-coated tablet contains:
Estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 1 mg.

Excipient with known effect: lactose monohydrate:
Each red film-coated tablet contains lactose monohydrate 37.3 mg
Each white film-coated tablet contains lactose monohydrate 37.9 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Red film-coated, biconvex tablets engraved with NOVO 282. Diameter: 6 mm.

White film-coated, biconvex tablets engraved with NOVO 283. Diameter: 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women with at least 6 months since last menses.

Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of or contraindicated for other medicinal products approved for the prevention of osteoporosis (see also section 4.4).

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Novofem is a continuous sequential HRT product for oral use. The oestrogen is dosed continuously. The progestagen is added for 12 days of every 28 day cycle, in a sequential manner.

One tablet is taken daily in the following order: oestrogen therapy (red film-coated tablet) over 16 days, followed by 12 days of oestrogen/progestagen therapy (white film-coated tablet).

After intake of the last white tablet, treatment is continued with the first red tablet of a new pack on the next day. A menstruation-like bleeding usually occurs at the beginning of a new treatment cycle.

In women who are not taking HRT or women in transition from a continuous combined HRT product, treatment with Novofem may be started on any convenient day. In women in transition from another

sequential HRT regimen, treatment should begin the day following completion of the preceding regimen.

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 combination product could be indicated if the response after 3 months is insufficient for symptom relief.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next 12 hours. If more than 12 hours have passed, the tablet should be discarded. 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 Novofem 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 contraindication 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 the 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.

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, 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 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 5) 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 HRT 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 venous thromboembolism 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 venous thromboembolism 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).

Hypothyroidism
Patients who require thyroid hormone replacement therapy should have their thyroid function monitored regularly while on HRT to ensure that thyroid hormone levels remain in an acceptable range.

Angioedema
Oestrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

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 radioimmunoassay) or T3 levels (by radioimmunoassay). 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.

Novofem tablets contain lactose monohydrate. 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, telaprevir 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.

Some laboratory tests may be influenced by oestrogen therapy, such as tests for glucose tolerance or thyroid function.

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

Concomitant administration of cyclosporine 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

Novofem is not indicated during pregnancy.

If pregnancy occurs during medication with Novofem, 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 those 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

Novofem is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Novofem has no known effect on the ability to drive or use machines.

4.8 Undesirable effects

Clinical experience

The most frequently reported adverse events during treatment in clinical trials conducted with an HRT product similar to Novofem were breast tenderness and headache (reported in ≥ 10% of patients).

The adverse events listed below may occur during oestrogen-progestagen treatment.

The frequencies are derived from clinical trials conducted with an HRT product similar to Novofem and from a Post-marketing Surveillance study on Novofem.

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		Vaginal candidiasis		
Immune system disorders				Allergic reaction
Psychiatric disorders				Nervousness
Nervous system	Headache	Dizziness	Migraine	Vertigo

disorders		Insomnia	Libido disorder NOS (not otherwise specified)	
		Depression		
Vascular disorders		Increased blood pressure. Aggravated hypertension	Peripheral embolism and thrombosis	
Gastrointestinal disorders		Dyspepsia	Vomiting	Diarrhoea
		Abdominal pain		Bloating
		Flatulence		
		Nausea		
Hepatobiliary disorders			Gall bladder disease	
			Gallstones	
Skin and subcutaneous tissue disorders		Rash	Alopecia	Acne
		Pruritus		
Musculoskeletal and connective tissue disorders			Muscle cramps	
Reproductive system and breast disorders	Breast tenderness	Vaginal haemorrhage		Uterine fibroid
		Uterine fibroids aggravated.		
General disorders and administration site conditions		Oedema		
Investigations		Weight increased		

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 Novofem treatment. Frequences of these adverse events cannot be estimated from the available data:

- Neoplasms benign and malignant (including cysts and polyps): Endometrial cancer
- Immune system disorders: Generalised hypersensitivity reactions (e.g. anaphylactic reaction/shock)
- Psychiatric disorders: Anxiety
- Nervous system disorders: Stroke
- Eye disorders: Visual disturbances
- Cardiac disorders: Myocardial infarction
- Vascular disorders: Hypertension aggravated
- Hepatobiliary disorders: Cholelithiasis aggravated, cholelithiasis recurrence
- Skin and subcutaneous tissue disorders: Seborrhoea, angioneurotic oedema, hirsutism
- Reproductive system and breast disorders: Endometrial hyperplasia, vulvovaginal pruritus
- Investigations: Weight decreased.

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:
- Skin and subcutaneous disorders: Chloasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, vascular purpura
- Probable dementia over the age of 65 (see section 4.4)
- Dry eyes

– Tear film composition changes.

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)	**Incidence per 1,000 never-users of HRTover 5 years**	**Risk ratio****	**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 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.

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' use (95% CI)**
CEE oestrogen-only			
50-79	21	0.8 (0.7-1.0)	-4 (-6-0)*
CEE+MPA oestrogen-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

The endometrial cancer risk is about 5 in every 1,000 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 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 the risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer risk

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 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 over 5 years' use (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 over 5 years' use (95% CI)**
50-59	8	1.3 (1.1-1.6)	3 (1-5)

* No differentiation was made between ischaemic and haemorrhagic stroke.

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.

4.9 Overdose

Symptoms of over dosage with oral oestrogens are breast tenderness, nausea, vomiting and/or metrorrhagia. Overdosage of progestagens may lead to a depressive mood, fatigue, acne and hirsutism. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestagens and oestrogens, sequential preparations, ATC code: G03FB05.

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 postmenopausal women and alleviates menopausal symptoms.

Oestrogens prevent bone loss following menopause or ovariectomy.

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

Relief of postmenopausal symptoms is achieved during the first few weeks of treatment.

In a post-marketing study regular withdrawal bleeding with a mean duration of 3-4 days occurred in 91% of women who took Novofem over 6 months. Withdrawal bleeding usually started a few days after the last tablet of the progestagen phase.

Oestrogen deficiency at menopause is associated with an increased bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysis of trials show that current use of HRT, oestrogen alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

Randomised, double-blind, placebo-controlled studies showed that 1 mg estradiol prevents the postmenopausal loss of bone minerals and increases the bone mineral density. The responses in the spine, femoral neck and trochanter were 2.8%, 1.6% and 2.5%, respectively, over 2 years with 1 mg 17ß-estradiol unopposed.

5.2 Pharmacokinetic properties

Following oral administration of 17β-estradiol in micronised form, rapid absorption from the gastrointestinal tract occurs. It undergoes extensive first-pass metabolism in the liver and other enteric organs, and a peak plasma concentration of approximately 27 pg/ml (range 13-40 pg/ml) occurs within 6 hours after intake of 1 mg. The area under the curve ($AUC_{(0\text{-}tz)}$)= 629 h x pg/ml. The half-life of 17β-estradiol is about 25 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 the gut but also in target organs, and involves the formation of less active or inactive metabolites, including oestrone, catecholoestrogens and several oestrogen sulfates and glucuronides. Oestrogens are excreted

with the bile, hydrolysed and reabsorbed (enterohepatic circulation), and mainly eliminated in urine in biologically inactive form.

After oral administration, 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 9 ng/ml (range 6-11 ng/ml) within 1 hour after intake of 1 mg. The area under the curve ($AUC_{(0-tz)}$) = 29 h x pg/ml. The terminal half-life of NET is about 10 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 sulfate 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

Animal studies with estradiol and norethisterone acetate have shown oestrogenic and progestagenic effects as expected. Both compounds induced adverse effects in preclinical reproductive toxicity studies, in particular embryotoxic effects and anomalies in urogenital tract development. Concerning other preclinic effects, the toxicity profiles of estradiol and norethisterone acetate are well-known and reveal no particular human risks beyond those discussed in other sections of the Summary of Product Characteristics and which generally apply to hormone substitution therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Both the white and the red tablets contain:

Lactose monohydrate
Maize starch
Hydroxypropylcellulose
Talc
Magnesium stearate

Film-coating

White film-coated tablet:
Hypromellose, triacetin and talc.

Red film-coated tablet:
Hypromellose, red iron oxide (E 172), titanium dioxide (E 171), propylene glycol and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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 it 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 and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

As registered locally.

8. MARKETING AUTHORISATION NUMBERS

As registered locally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 September 2000

10. DATE OF REVISION OF THE TEXT

MM/YYYY

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Novofem film-coated tablets
Estradiol/norethisterone acetate

2. STATEMENT OF ACTIVE SUBSTANCES

Each red tablet contains estradiol 1 mg (as estradiol hemihydrate)
Each white tablet contains estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 1 mg

3. LIST OF EXCIPIENTS

Excipients include lactose monohydrate. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 28 (16 red and 12 white) film-coated tablets
3 x 28 (16 red and 12 white) film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Novofem

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DISPENSER LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Novofem film-coated tablets
Estradiol/norethisterone acetate
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

28 film-coated tablets

6. OTHER

16 red tablets: estradiol 1 mg (as estradiol hemihydrate)
12 white tablets: estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 1 mg
Excipients include lactose monohydrate. See leaflet for further information

7. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

PACKAGE LEAFLET

Package leaflet: Information for the user

Novofem film-coated tablets
Estradiol/norethisterone acetate

Read this entire leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Novofem is and what it is used for

Novofem is a sequential combined Hormone Replacement Therapy (HRT) which is taken every day without interruption. Novofem is used in postmenopausal women with at least 6 months since their last natural period.

Novofem contains 2 hormones, an oestrogen (estradiol) and a progestagen (norethisterone acetate). The estradiol in Novofem is identical to the estradiol produced in the ovaries of women, and is classified as a natural oestrogen. Norethisterone acetate is a synthetic progestagen, which acts in a similar manner as progesterone, another important female sex hormone.

Novofem is used for:

Relief of symptoms occurring after menopause
During the menopause, the amount of the oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ('hot flushes'). Novofem alleviates these symptoms after menopause. You will only be prescribed Novofem if your symptoms seriously hinder your daily life.

Prevention of osteoporosis
After the menopause some women may develop fragile bones (osteoporosis). You should discuss all available options with your doctor.
If you are at an increased risk of fractures due to osteoporosis and other medicines are not suitable for you, you can use Novofem to prevent osteoporosis after menopause.

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

2. What you need to know before you take Novofem

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

The experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited. If you have a premature menopause the risks of using HRT may be different. Please talk to your doctor.

Before you start (or restart) HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or an internal examination, if necessary.

Once you have started on Novofem, you should see your doctor for regular check-ups (at least once a year). At these check-ups, discuss with your doctor the benefits and risks of continuing with Novofem.

Go for regular breast screening, as recommended by your doctor.

Do not take Novofem
If any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before taking Novofem.
Do not take Novofem:
- If you have, have had or suspect having **breast cancer.**
- If you have, have had or suspect having **cancer of the womb lining** (endometrial cancer), or any other oestrogen dependent cancer.
- If you have any **unexplained vaginal bleeding.**
- If you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated.
- If you have or have ever had a **blood clot in a vein** (venous thromboembolism), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism).
- If you have a **blood clotting disorder** (such as protein C, protein S or antithrombin deficiency).
- If you have or previously have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina.**
- If you have or have ever had a **liver disease** and your liver function tests have not returned to normal.
- If you are **allergic** (hypersensitive) to **estradiol**, **norethisterone acetate** or any of the other ingredients of Novofem (listed in section 6 'Contents of the pack and other information').
- If you have a **rare blood problem called 'porphyria'** which is passed down in families (inherited).

If any of the above conditions appear for the first time while taking Novofem, stop taking it at once and consult your doctor immediately.

Warnings and precautions
Tell your doctor if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with Novofem. If so, you should see your doctor more often for check-ups:
- fibroids inside your womb
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia)
- increased risk of developing blood clots (see 'Blood clots in a vein (venous thromboembolism)')
- increased risk of getting a oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)
- high blood pressure
- a liver disorder, such as a benign liver tumour
- diabetes

- gallstones
- migraine or severe headaches
- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE)
- epilepsy
- asthma
- a disease affecting the eardrum and hearing (otosclerosis)
- a very high level of fat in your blood (triglycerides)
- fluid retention due to cardiac or kidney problems
- a condition where your thyroid gland fails to produce enough thyroid hormone (hypothyroidism) and you are treated with thyroid hormone replacement therapy
- a hereditary condition causing recurrent episodes of severe swelling (hereditary angioedema) or if you have had episodes of rapid swelling of the hands, face, feet, lips, eyes, tongue, throat (airway blockage) or digestive tract
- lactose intolerance.

Stop taking Novofem and see a doctor immediately
If you notice any of the following when taking HRT:
- any of the conditions mentioned in the 'Do not take Novofem' section.
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease.
- a large rise in your blood pressure (symptoms may be headache, tiredness and dizziness).
- migraine-like headaches which happen for the first time.
- if you become pregnant.
- if you notice signs of a blood clot, such as:
  - painful swelling and redness of the legs
  - sudden chest pain
  - difficulty in breathing.

  For more information, see 'Blood clots in a vein (venous thromboembolism)'.

Note: Novofem is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)
Taking oestrogen-only HRT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).

The progestagen in Novofem protects you from this extra risk.

Compare
In women who still have a womb and who are not taking HRT, on average, 5 in 1,000 will be diagnosed with endometrial cancer between the ages of 50 and 65.

For women aged 50 to 65 who still have a womb and who take oestrogen-only HRT, between 10 and 60 women in 1,000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it is taken.

Unexpected bleeding
You will have a bleed once a month (so-called withdrawal bleed) while taking Novofem. But, if you have unexpected bleeding or drops of blood (spotting) besides your monthly bleeding, which:
- carries on for more than the first 6 months

- starts after you have been taking Novofem more than 6 months
- carries on after you have stopped taking Novofem

see your doctor as soon as possible.

Breast cancer
Evidence suggests that taking combined oestrogen-progestagen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

Compare
Women aged 50 to 79 who are not taking HRT, on average, 9 to 17 in 1,000 will be diagnosed with breast cancer over a 5-year period.

For women aged 50 to 79 who are taking oestrogen-progestagen HRT over 5 years, there will be 13 to 23 cases in 1,000 users (i.e. an extra 4 to 6 cases).

Regularly check your breasts. See your doctor if you notice any changes such as:
- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel.

Ovarian cancer
Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years.

Women aged 50 to 69 who are not taking HRT, on average, about 2 women in 1,000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years there will be between 2 and 3 cases per 1,000 users (i.e. up to 1 extra case).

Effect of HRT on heart and circulation

Blood clots in a vein (venous thromboembolism)
The risk of **blood clots in the veins** is about 1.3 to 3 times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:
- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, 'If you need to have surgery').
- you are seriously overweight (BMI >30 kg/m²).
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots.
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ.
- you have systemic lupus erythematosus (SLE).
- you have cancer.

For signs of a blood clot, see 'Stop taking Novofem and see a doctor immediately'.

Compare
Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1,000 would be expected to get a blood clot in a vein.

For women in their 50s who have been taking oestrogen-progestagen HRT for over 5 years, there will be 9 to 12 cases in 1,000 users (i.e. an extra 5 cases).

Heart disease (heart attack)
There is no evidence that HRT will prevent a heart attack. Women over the age of 60 years who use oestrogen-progestagen HRT are slightly more likely to develop heart disease than those not taking any HRT.

Stroke
The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare
Looking at women in their 50s who are not taking HRT, on average, 8 in 1,000 would be expected to have a stroke over a 5-year period.

For women in their 50s who are taking HRT, there will be 11 cases in 1,000 users over 5 years (i.e. an extra 3 cases).

Other conditions
HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Using other medicines
Some medicines may interfere with the effect of Novofem. This might lead to irregular bleeding. This applies to the following medicines:
- Medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepine)
- Medicines for **tuberculosis** (such as rifampicin and rifabutin)
- Medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- Medicines for **hepatitis C infections** (such as telaprevir)
- Herbal remedies containing **St John's Wort** (*Hypericum perforatum*).

Other medicines may increase the effects of Novofem:
- Medicines containing **ketoconazole** (a fungicide).

Novofem may have an impact on a concomitant treatment with cyclosporine.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription, herbal medicines or other natural products.

Laboratory tests
If you need a blood test, tell your doctor or the laboratory staff that you are taking Novofem, because this medicine can affect the results of some tests.

Taking Novofem with food and drink
The tablets can be taken with or without food and drink.

Pregnancy and breast-feeding
Pregnancy: Novofem is for use in postmenopausal women only. If you become pregnant, stop taking Novofem and contact your doctor.

Breast-feeding: You should not take Novofem if you are breast-feeding.

Driving and using machines

Novofem has no known effect on the ability to drive or use machines.

Important information about some of the ingredients in Novofem
Novofem contains lactose monohydrate. If you have an intolerance to some sugars, contact your doctor before taking Novofem.

3. How to take Novofem

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are unsure.

If you are not switching from another hormone replacement therapy you can start treatment with Novofem on any convenient day. If you are switching from another hormone replacement therapy ask your doctor when you should start treatment with Novofem.

Take one tablet once a day, at about the same time each day.
Each pack contains 28 tablets
Days 1 – 16 **Take one red** tablet every day for 16 days
Days 17 – 28 **Take one white** tablet every day for 12 days

Take the tablets with a glass of water.

Once you have finished the pack, start a new pack continuing the treatment without interruption. A menstruation-like bleeding (period) usually occurs at the beginning of a new pack.

For further information on the use of the calendar pack, see USER INSTRUCTIONS at the end of the package leaflet.

Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

Talk to your doctor if you do not experience symptom relief after 3 months of treatment. You should only continue treatment as long as the benefit outweighs the risk.

If you take more Novofem than you should
If you have taken more Novofem than you should, talk to a doctor or pharmacist. An overdose of oestrogens may cause breast tenderness, nausea, vomiting and/or irregular vaginal bleeding (metrorrhagia). Overdosage of progestagens may lead to depressive mood, fatigue, acne and growth of body or facial hair (hirsutism).

If you forget to take Novofem
If you forget to take your tablet at the usual time, take it within the next 12 hours. If more than 12 hours have gone by, start again as normal the next day. Do not take a double dose to make up for a forgotten tablet.

Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

If you stop taking Novofem
If you would like to stop taking Novofem, talk to your doctor first. Your doctor will explain the effects of stopping treatment and discuss other possibilities with you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you need to have surgery

If you are going to have surgery, tell the surgeon that you are taking Novofem. You may need to stop taking Novofem about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2, 'Blood clots in a vein (venous thromboembolism)'). Ask your doctor when you can start taking Novofem again.

4. Possible side effects

Like all medicines, this medicine can have side effects, although not everybody gets them.

The following diseases are reported more often in women using HRT compared to women not using HRT:
- breast cancer
- abnormal growth or cancer of the lining of the womb (endometrial hyperplasia or cancer)
- ovarian cancer
- blood clots in the veins of the legs or lungs (venous thromboembolism)
- heart disease
- stroke
- probable memory loss if HRT is started over the age of 65.

For more information about these side effects, see section 2, 'What you need to know before you take Novofem'.

Hypersensitivity/allergy (uncommon side effect – affects 1 to 10 users in 1,000)
Though it is an uncommon event, hypersensitivity/allergy may occur. Signs of hypersensitivity/allergy may include one or more of the following symptoms: hives, itching, swelling, difficulty in breathing, low blood pressure (paleness and coldness of skin, rapid heartbeat), feeling dizzy, sweating, which could be signs of anaphylactic reaction/shock. If one of the mentioned symptoms appears, **stop taking Novofem and seek immediate medical help.**

Very common side effects (may affect more than 1 in 10 people)
- Headache
- Breast tenderness.

Common side effects (may affect up to 1 in 10 people)
- Increased blood pressure, aggravated hypertension
- Vaginal infection with a fungus (e.g. thrush)
- Dizziness, sleeplessness, depression
- Dyspepsia (indigestion), abdominal pain, flatulence
- Nausea (feeling sick)
- Rash, itching
- Vaginal bleeding (see section 2 subsection 'Unexpected bleeding')
- Aggravation of uterine fibroids (benign tumour of the womb)
- Oedema (swelling of hands, ankles and feet)
- Weight increase.

Uncommon side effects (may affect up to 1 in 100 people)
- Migraine
- Changes in libido (changes in sexual desire)
- Peripheral embolism and thrombosis (blood clot)
- Vomiting (being sick)
- Gall bladder disease or gallstones
- Hair loss (alopecia)
- Muscle cramps.

Rare side effects (may affect up to 1 in 1,000 people)
- Allergic reactions
- Nervousness
- Vertigo (dizziness)
- Diarrhoea
- Bloating
- Acne
- Uterine fibroid (benign tumour of the womb).

Not known (frequency cannot be estimated from the available data)
- Endometrial hyperplasia (excessive growth of the lining of the womb)
- Increased body and facial hair
- Anxiety
- Visual disturbances
- Seborrhoea
- Vaginal itching.

Other side effects of combined HRT
The following side effects have been reported with other HRTs:
- Various skin disorders:
  - discolouration of the skin especially of the face or neck known as 'pregnancy patches' (chloasma)
  - painful reddish skin nodules (erythema nodosum)
  - rash with target-shaped reddening or sores (erythema multiforme)
  - red or purple discolorations of the skin and/or mucous membranes (vascular purpura)
- Dry eyes
- Tear film composition changes.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Novofem

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label and outer carton after 'EXP'. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Novofem contains
- The active substances are estradiol and norethisterone acetate.
  The red film-coated tablets contain: estradiol 1 mg (as estradiol hemihydrate).

The white film-coated tablets contain: estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 1 mg.

– The other ingredients are: lactose monohydrate, maize starch, hydroxypropylcellulose, talc and magnesium stearate.
Film-coating (red tablets) contains: hypromellose, talc, titanium dioxide (E171), propylene glycol and red iron oxide (E172).
Film-coating (white tablets) contains: hypromellose, triacetin and talc.

What Novofem looks like and contents of the pack
The film-coated tablets are round with a diameter of 6 mm. The red tablets are engraved with NOVO 282. The white tablets are engraved with NOVO 283.

Each pack of 28 tablets contains 16 red tablets and 12 white tablets.

Pack sizes available:
1 x 28 film-coated tablets
3 x 28 film-coated tablets
Not all pack sizes may be marketed.
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
[To be completed nationally]

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

This medicinal product is authorised in the Member States of the EEA under the following names:
Member States of the EEA: Novofem – except for
France: Novofemme
Spain: Duofemme

This leaflet was last revised in: DDMMYYYY

Other sources of information
Detailed information on this medicine is available on the website of {MA/Agency}

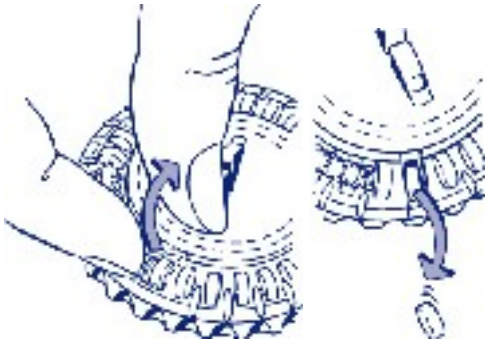
USER INSTRUCTIONS

How to use the calendar pack

1. Set the day reminder
Turn the inner disc to set the day of the week opposite the little plastic tab.

2. Take the first day's tablet

Break the plastic tab and tip out the first tablet.



3. Move the dial every day

On the next day simply move the transparent dial clockwise 1 space as indicated by the arrow. Tip out the next tablet. Remember to take only 1 tablet once a day.

You can only turn the transparent dial after the tablet in the opening has been removed.