Novofem®

Film-coated tablets

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.

Tablet core contains:
Lactose monohydrate, maize starch, hydroxypropylcellulose, talc and magnesium stearate.

Film-coating:
White tablets: Hypromellose, triacetin and talc.
Red tablets: Hypromellose, red iron oxide (E172), titanium dioxide (E171), propylene glycol and talc.
White film-coated, biconvex tablets are engraved with NOVO 283 and the red film-coated, biconvex tablets are engraved with NOVO 282.
Diameter: 6 mm.

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

Therapeutic indications
Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women 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 *Special warnings and precautions for use*).
The experience treating women older than 65 years is limited.

Posology and method of administration
Novofem® is a continuous sequential preparation for hormone replacement therapy. 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 transferring from a continuous combined HRT product, treatment may be started on any convenient day. In women transferring from another sequential HRT regimen, treatment should begin the day following completion of the prior regimen.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also *Special warnings and precautions for use*) should be used. A switch to a higher dose combination product could be indicated if the response after 3 months is insufficient for satisfactory 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 is to be discarded. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

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 idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency (see *Special warnings and precautions for use*))
- 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.

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.

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 *Undesirable effects*). 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 *Special warnings and precautions for use*).
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 *Undesirable effects*). Some studies, including the WHI trial, suggest that the long-term use of combined HRTs may confer a similar or slightly smaller risk (see *Undesirable effects*).

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 *Undesirable effects*).
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 *Contraindications*).
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 *Undesirable effects*).

Other conditions
Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
Oestrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.
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, 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.

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 Novofem®.
Concomitant administration of cyclosporine may cause increased blood levels of cyclosporine, creatinine and transaminases due to decreased metabolism of cyclosporine in the liver.
Reduced estradiol levels have been observed under the simultaneous use of antibiotics e.g. penicillins and tetracycline.

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 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.

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

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®.

Very common: ≥1/10
Nervous system disorders:
- Headache

Reproductive system and breast disorders:
- Breast tenderness

Common: ≥1/100; <1/10
Infections and infestations:
- Vaginal candidiasis

Nervous system disorders:
- Dizziness
- Insomnia
- Depression

Vascular disorders:
- Increased blood pressure
- Aggravated hypertension

Gastrointestinal disorders:
- Dyspepsia
- Abdominal pain
- Flatulence
- Nausea

Skin and subcutaneous tissue disorders:
- Rash
- Pruritus

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Reproductive system and breast disorders:
- Vaginal haemorrhage
- Uterine fibroids aggravated

General disorders and administration site conditions:
- Oedema

Investigations:
- Weight increased

Uncommon: ≥1/1,000; <1/100
Nervous system disorders:
- Migraine
- Libido disorder NOS (not otherwise specified)

Vascular disorders:
- Peripheral embolism and thrombosis

Gastrointestinal disorders:
- Vomiting

Hepatobiliary disorders:
- Gallbladder disease
- Gallstones

Skin and subcutaneous tissue disorders:
- Alopecia

Musculoskeletal and connective tissue disorders:
- Muscle cramps

Rare: ≥1/10,000; <1/1,000
Immune system disorders:
- Allergic reaction

Psychiatric disorders:
- Nervousness

Nervous system disorders:
- Vertigo

Gastrointestinal disorders:
- Diarrhoea
- Bloating

Skin and subcutaneous tissue disorders:
- Acne

Reproductive system and breast disorders:
- Uterine fibroid

Post-marketing experience
In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgment 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: 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 recurrence
- Skin and subcutaneous tissue disorders: Seborrhoea, rash, angioneurotic oedema
- Reproductive system and breast disorders: Hyperplasia of endometrium, vulvovaginal pruritus
- Investigations: Weight decreased, blood pressure increased.

Other adverse reactions have been reported in association with oestrogen-progestagen treatment:
- Skin and subcutaneous disorders: Alopecia, chloasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, vascular purpura
- Probable dementia over the age of 65 (see also *Special warnings and precautions for use*).

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 *Special warnings and precautions for use*).
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

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

Combined oestrogen-progestagen
Age range (years): 50-65
Additional cases per 1,000 never-users of HRT over a 5-year period*: 9-12
Risk ratio **: 1.7
Additional cases per 1,000 HRT users over 5 years use (95%CI): 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

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

CEE+MPA oestrogen-progestagen**
Age range (years): 50-79
Incidence per 1,000 women in placebo arm over 5 years: 14
Risk ratio and 95%CI: 1.2 (1.0-1.5)
Additional cases per 1,000 HRT users over 5 years (95%CI): 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 also *Special warnings and precautions for use*).
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 also *Special warnings and precautions for use*). Results of the WHI studies are presented below:

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

Oral oestrogen-only*
Age range (years): 50-59
Incidence per 1,000 women in placebo arm over 5 years: 7
Risk ratio and 95%CI: 1.2 (0.6-2.4)
Additional cases per 1,000 HRT users over 5 years (95%CI): 1 (-3-10)

Oral combined oestrogen-progestagen
Age range (years): 50-59
Incidence per 1,000 women in placebo arm over 5 years: 4
Risk ratio and 95%CI: 2.3 (1.2-4.3)
Additional cases per 1,000 HRT users over 5 years (95%CI): 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 also *Special warnings and precautions for use*).

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 *Special warnings and precautions for use*).

WHI Studies Combined – Additional risk of ischaemic stroke* over 5 years' use
Age range (years): 50-59
Incidence per 1,000 women in placebo arm over 5 years: 8
Risk ratio and 95%CI: 1.3 (1.1-1.6)
Additional cases per 1,000 HRT users over 5 years (95%CI): 3 (1-5)

* No differentiation was made between ischaemic and haemorrhagic stroke.

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

Pharmacological properties
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 menopausal 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 greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.
Relief of menopausal symptoms is achieved during the first few weeks of treatment.
In a post-marketing study regular withdrawal bleeding with a mean duration of three to four 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 increasing 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-analysed trials shows that current use of HRT, 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.

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×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. 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 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. Oestrogens are partly excreted by 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 a peak plasma concentration of approximately 9 ng/ml (range 6-11 ng/ml) occurs within 1 hour after intake of 1 mg. The area under the curve ($AUC_{(0\text{-}tz)}$) = 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 sulphate or glucuronide conjugates.
The pharmacokinetic properties in the elderly have not been studied.

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

Incompatibilities
Not applicable.

Special precautions for storage
Store below 30°C. Do not refrigerate. Keep the container in the outer carton in order to protect from light.

Nature and contents of container
1×28 tablets or 3×28 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.

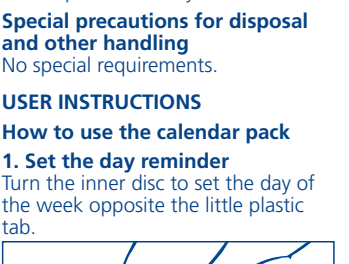
Not all pack sizes may be marketed.

Special precautions for disposal and other handling
No special requirements.

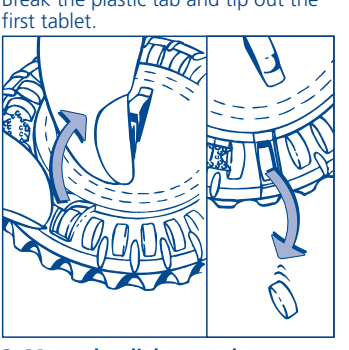
USER INSTRUCTIONS

How to use the calendar pack

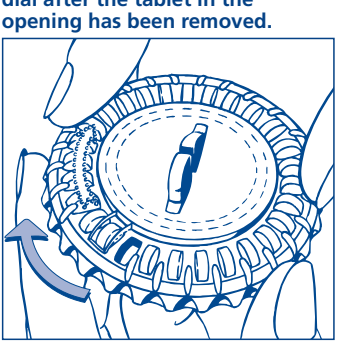
1. Set the day reminder
Turn the inner disc to set the day of the week opposite the little plastic tab.



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.



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