Activelle®

film-coated tablets

Each Activelle® film-coated tablet contains estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 0.5 mg.

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

Film-coating:
Hypromellose, triacetin, talc.
The tablets are white film-coated, round, biconvex tablets with a diameter of 6 mm. The tablets are engraved with NOVO 288 on one side and APIS on the other side.

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

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

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

Posology and method of administration
Activelle® is a continuous combined hormone replacement product 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 "Special warnings and precautions for use") should be used.
A switch to a higher dose combination product could be indicated 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 Activelle 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 one tablet, the forgotten 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 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)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- 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 (please see the "Breast Cancer" section below).
Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision
If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Activelle, in particular:
- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or 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 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
The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see also "Undesirable effects"). The addition of a progestagen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.
Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer
A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestagen combinations or tibolone for HRT for several years (see also "Undesirable effects").
For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.
In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regardless of type of progestagen. There was no evidence of a difference in risk between the different routes of administration.
In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.
HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism
HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate =4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate =9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.
Generally recognised risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism, or recurrent spontaneous abortion, should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.
If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)
There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke
One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer
Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRTs confers to a different risk than oestrogen-only products.

Other conditions
Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Activelle will increase.
Women with pre-existing hypertriglyceridemia 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-l-antitrypsin, ceruloplasmin).
There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.
Activelle contains lactose. 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 metabolizing enzymes e.g. ketoconazole, may increase circulating levels of the active substances in Activelle.

Pregnancy and lactation
Activelle is not indicated during pregnancy.
If pregnancy occurs during medication with Activelle, treatment should be withdrawn immediately.
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
Activelle is not indicated during lactation.

Effects on ability to drive and use machines
No effects known.

Undesirable effects
Clinical experience
The most frequently reported adverse events in the clinical trials with Activelle were vaginal bleeding and breast pain/tenderness, reported in approximately 10% to 20% of patients. Vaginal bleeding usually occurred in the first months of treatment. Breast pain usually disappears after a few months of therapy. All adverse events observed with a higher frequency in patients treated with Activelle as compared

to placebo and which on an overall judgement are possible related to treatment are presented below.

Very common: >1/10 (more than 1 per 10)
Reproductive system and breast disorders:
- Breast pain or beast tenderness
- Vaginal haemorrhage.

Common: >1/100 and <1/10 (more than 1 per 100 and less than 1 per 10)
Infections and infestations:
- Genital candidiasis or vaginitis (see also "Reproductive system and breast disorders").

Metabolism and nutrition disorders:
- Fluid retention (se also "General disorders and administration on site conditions").

Psychiatric disorders:
- Depression or depression aggravated.

Nervous system disorders:
- Headache
- Migraine or migraine aggravated.

Gastrointestinal disorders:
- Nausea.

Musculoskeletal, connective tissue and bone disorders:
- Back pain.

Reproductive system and breast disorders:
- Breast oedema or breast enlargement
- Uterine fibroids aggravated or uterine fibroids reoccurrence or uterine fibroids.

General disorders and administration site conditions:
- Oedema peripheral.

Investigations
- Weight increased.

Uncommon: >1/1,000 and <1/100 (more than 1 per 1,000 and less than 1 per 100)
Immune system disorders:
- Hypersensitivity (see also "Skin and subcutaneous tissue disorders").

Psychiatric disorders:
- Nervousness.

Vascular disorders:
- Thrombophlebitis superfecial.

Gastrointestinal disorders:
- Abdominal pain
- Abdominal distension
- Abdominal discomfort
- Flatulence or bloating.

Skin and subcutaneous tissue disorders:
- Alopecia
- Hirsutism or acne
- Pruritus or urticaria.

Musculoskeletal, connective tissue and bone disorders:
- Leg cramps.

General disorders and administration site conditions:
- Drug ineffective.

Rare: >1/10,000 and < 1/1,000 (more than 1 per 10,000 and less 1 per 1,000):
Vascular disorders:
- Pulmonary embolism
- Thrombophlebitis deep.

Breast cancer
According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.
For oestrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI: 1.21 – 1.49) and 1.30 (95%CI: 1.21 – 1.40), respectively.
For oestrogen plus progestagen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.
The MWS reported that, compared to never users, the use of various types of oestrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).
The WHI trial reported a risk estimate of 1.24 (95%CI: 1.01 – 1.54) after 5.6 years of use of oestrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.
The absolute risks calculated from the MWS and the WHI trials are presented below:
The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:
- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years
- For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be:
  For users of oestrogen-only replacement therapy
  between 0 and 3 (best estimate = 1.5) for 5 years use
  between 3 and 7 (best estimate = 5) for 10 years use.
  For users of oestrogen plus progestagen combined HRT,
  between 5 and 7 (best estimate = 6) for 5 years use
  between 18 and 20 (best estimate = 19) for 10 years use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an additional 8 cases of invasive breast cancer would be due to oestrogen-progestagen combined HRT (CEE + MPA) per 10,000 women years.
According to calculations from the trial data, it is estimated that:
- For 1000 women in the placebo group:
- about 16 cases of invasive breast cancer would be diagnosed in 5 years
- For 1000 women who used oestrogen + progestagen combined HRT (CEE + MPA), the number of additional cases would be between 0 and 9 (best estimate = 4) for 5 years use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see also "Special warnings and precautions for use").

Endometrial cancer
In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.

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 treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (<1/10,000 patient years). 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:
- Neoplasmas benign and malignant (incl. cysts and polyps): Endometrial cancer.
- Psychiatric disorders: Insomnia, anxiety, libido decreased, libido increased.
- Nervous system disorders: Dizziness, stroke.
- Eye disorders: Visual disturbances.
- Vascular disorders: Hypertension aggravated.
- Cardiac disorders: Myocardial infarction.
- Gastrointestinal disorders: Dyspepsia, vomiting.
- Hepatobilitary disorders: Gallbladder disease, cholelithiasis, cholelithiasis aggravated, cholelithiasis re-occurrence.
- Skin and subcutaneous tissue disorder: Seborrhoea, rash, angioneurotic oedema .
- Reproductive system and breast disorders: Hyperplasia endometrial, vulvovaginal pruritus.
- Investigations: Weight decreased, blood pressure increased.

The following adverse reactions have been reported in association with other oestrogen/progestagen treatment:
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia (see also "Special warnings and precautions for use").

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

Pharmacodynamic properties
ATC code G03F A01
Oestrogen and progestagen for continuous combined hormone replacement therapy (HRT).
Estradiol: The active ingredient, synthetic 17ß-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: 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.
Activelle is a continuous combined HRT given with the intent of avoiding the regular withdrawal bleeding associated with cyclic or sequential HRT. Amenorrhoea (no bleeding and spotting) was seen in 90% of the women during months 9-12 of treatment. Bleeding and/or spotting appeared in 27% of the women during the first three months of treatment and in 10% during months 10-12 of treatment.
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.
The effect of oestrogen on bone mineral density is dose dependent and therefore, the effect of Activelle may be less than observed with higher doses of estradiol. The effects of Activelle on bone mineral density were examined in two 2-year, randomized, double-blind, placebo-controlled clinical trials in postmenopausal women (n=327 in one trial, including 47 on Activelle and 48 on Kliogest® (2 mg estradiol and 1 mg norethisterone acetate); and n=135 in the other trial, including 46 on Activelle). All women received calcium supplementation ranging from 500 to 1000 mg daily. Activelle significantly prevented bone loss at the lumbar spine, total hip, distal radius and total body in comparison with calcium supplemented placebo-treated women. In early postmenopausal women (1 to 5 years since last menses), the percentage change from baseline in bone mineral density at lumbar spine, femoral neck and femoral trochanter in patients completing 2 years of treatment with Activelle was 4.8±0.6%, 1.6±0.7% and 4.3±0.7% (mean±SEM), respectively, while with the higher dose combination containing 2 mg E_2 and 1 mg NETA (Kliogest) it was 5.4±0.7%, 2.9±0.8% and 5.0±0.9%, respectively. The percentage of women who maintained or gained bone mineral density during treatment with Activelle and Kliogest was 87% and 91%, respectively, after 2 years of treatment. In a study conducted in postmenopausal women with a mean age of 58 years, treatment with Activelle for 2 years increased the bone mineral density at lumbar spine by 5.9±0.9%, at total hip by 4.2±1.0%, at distal radius by 2.1±0.6%, and at total body by 3.7±0.6%. In these women, Activelle decreased bone resorption and bone formation markers to mean values within the premenopausal range.

Pharmacokinetic properties
Following oral administration of 17ß-estradiol in micronized form, rapid absorption from the gastrointestinal tract occurs. It undergoes extensive first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 35 pg/ml (range 21-52 pg/ml) within 5-8 hours. The half-life of 17ß-estradiol is about 12-14 hours. It circulates bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound. Metabolism of 17ß-estradiol, occurs mainly in the liver and gut but also in target organs, and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several oestrogen sulphates and glucuronides. Oestrogens are excreted with the bile, where they are hydrolysed and reabsorbed (enterohepatic circulation), and mainly 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 3.9 ng/ml (range 1.4-6.8 ng/ml) within 0.5 -1.5 hour. The terminal half-life of NET is about 8-11 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 sulfate or glucuronide conjugates.
The pharmacokinetics in the elderly have not been studied.

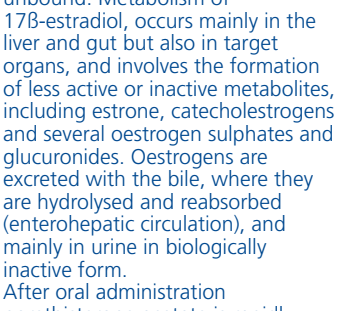
Preclinical safety data
The toxicity profiles of estradiol and norethisterone acetate are well known. There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections.

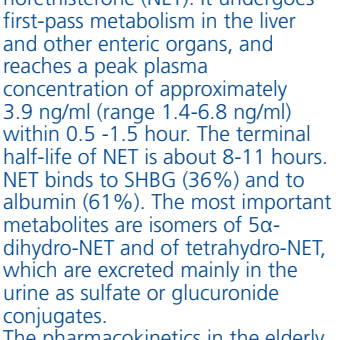
Incompatibilities
Not applicable.

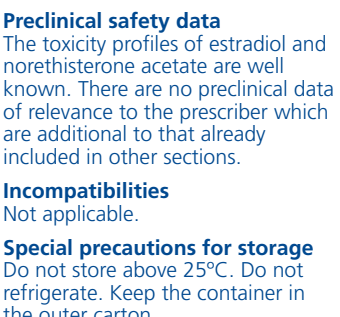
Special precautions for storage
Do not store above 25°C. Do not refrigerate. Keep the container in the outer carton.

Nature and contents of container
1x28 tablets or 3x28 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.

Instructions for use

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


2. How to take the first tablet
Break the plastic tab and tip out the first tablet.


3. Every day
Simply move the transparent dial clockwise one space as indicated by the arrow. Tip out the next tablet. The transparent dial can only be turned after the tablet in the opening has been removed.

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