Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Activelle 1 mg/0.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 0.5 mg.

Excipient with known effect: Each film-coated tablet contains lactose monohydrate 37.0 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

White film-coated, round, biconvex tablets with a diameter of 6 mm. The tablets are engraved with NOVO 288 on one side and the Apis bull on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women with more than 1 year 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.

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Activelle is a continuous combined HRT 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 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.

In women with amenorrhoea and not taking HRT or women in transition from another continuous combined HRT product, treatment with Activelle may be started on any convenient day. In women in transition from a sequential HRT regimen, treatment should start right after their withdrawal bleeding has ended.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next 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 Activelle 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 more than 10 years.

The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting continues after the first months of treatment, appears after some time during therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestagen or 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 a meta-analysis of prospective 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 (1-4) years (see section 4.8).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

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. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.
Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with 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/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at a young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects), HRT is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT.

The relative risk of CAD during use of combined oestrogen-progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen-progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic stroke

Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Other conditions

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

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

Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

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.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than

ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5.

Activelle tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total 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, carbamazepine) 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.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

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

Concomitant administration of cyclosporine and Activelle 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
Activelle is not indicated during pregnancy.
If pregnancy occurs during medication with Activelle, 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
Activelle is not indicated during lactation.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

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

4.8 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 disappeared after a few months of therapy. All adverse events observed in the randomised clinical trials with a higher frequency in patients treated with Activelle as compared to placebo, and which on an overall judgement are possibly related to treatment, are presented in the table below.

System organ class	**Very common ≥ 1/10**	**Common ≥ 1/100; < 1/10**	**Uncommon ≥ 1/1,000; < 1/100**	**Rare ≥ 1/10,000; < 1/1,000**
Infections and infestations		Genital candidiasis or vaginitis, see also Reproductive system and breast disorders		
Immune system disorders			Hypersensitivity, see also, Skin and subcutaneous tissue disorders	
Metabolism and nutrition disorders		Fluid retention, see also, General disorders and administration site conditions		
Psychiatric disorders		Depression or depression aggravated	Nervousness	
Nervous system disorders		Headache, migraine or migraine aggravated		
Vascular disorders			Thrombophlebitis superficial	Deep venous thromboembolism Pulmonary embolism
Gastrointestinal disorders		Nausea	Abdominal pain, abdominal distension or abdominal discomfort Flatulence or bloating	
Skin and subcutaneous tissue disorders			Alopecia, hirsutism or acne Pruritus or urticaria	
Musculoskeletal and connective tissue disorders		Back pain	Leg cramps	
Reproductive system and	Breast pain or breast	Breast oedema or breast enlargement Uterine fibroids aggravated or uterine fibroids		

breast disorders	tenderness Vaginal haemorrhage	reoccurrence or uterine fibroids		
General disorders and administration site conditions		Oedema peripheral	Drug ineffective	
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 Activelle treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (< 1/10,000, not known (cannot be estimated from the available data)). Post-marketing experience is subject to underreporting especially with regard to trivial and well-known adverse drug reactions. The presented frequencies should be interpreted in that light:

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

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:
– Skin and subcutaneous tissue disorders: Alopecia, chloasma, erythema multiforme, erythema nodosum, vascular purpura
– Probable dementia over the age of 65 (see section 4.4).

Breast cancer risk

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
The increased risk in users of oestrogen-only therapy is 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).

Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented below:

Largest meta-analysis of prospective epidemiological studies

Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	**Incidence per 1,000 never-users of HRT over a 5 year period (50-54 years)***	**Risk ratio**	**Additional cases per 1,000 HRT users after 5 years**
Oestrogen-only HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestagen			

50	13.3	1.6	8.0

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	**Incidence per 1,000 never-users of HRT over a 10 year period (50-59 years)***	**Risk ratio**	**Additional cases per 1,000 HRT users after 10 years**
Oestrogen-only HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestagen			
50	26.6	1.8	20.8

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).
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

Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).
A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period.

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 HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 with actions similar to those of progesterone, a natural female sex hormone. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Pharmacodynamic effects

In clinical trials with Activelle, the addition of the norethisterone acetate component enhanced the vasomotor symptom relieving effect of 17β-estradiol.

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 or spotting) was seen in 90% of the women during months 9-12 of treatment. Bleeding and/or spotting was observed in 27% of the women during the first 3 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 effects of Activelle on bone mineral density were examined in 2 two-year, randomised, 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 1,000 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%.

5.2 Pharmacokinetic properties

Absorption and distribution of 17β-estradiol

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 reaches a peak plasma concentration of approximately 35 pg/ml (range 21-52 pg/ml) within 5-8 hours. The half-life of 17β-estradiol is about 12-14 hours. It circulates bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound.

Biotransformation and elimination of 17β-estradiol

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.

Absorption and distribution of norethisterone acetate

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 hours. The terminal half-life of NET is about 8-11 hours. NET binds to SHBG (36%) and to albumin (61%).

Biotransformation and elimination of norethisterone acetate

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 pharmacokinetic properties in the elderly have not been studied.

5.3 Preclinical safety data

The acute toxicity of oestrogens is low. Because of marked differences between animal species and between animals and humans, preclinical results possess a limited predictive value for the application of oestrogens in humans.

In experimental animals, estradiol or estradiol valerate displayed an embryolethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male foetuses were observed.

Norethisterone, like other progestagens, caused virilisation of female foetuses in rats and monkeys. After high doses of norethisterone, embryolethal effects were observed.

Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risks beyond those discussed in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Copovidone
Talc
Magnesium stearate

Film-coating:
Hypromellose
Triacetin
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

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

8 MARKETING AUTHORISATION NUMBER

PA0218/052/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 1998
Date of last renewal: 6th March 2013

10 DATE OF REVISION OF THE TEXT

September 2024