Professional Information

S4 Activelle®
Film-coated tablets

Scheduling status
S4

1 Name of the medicine
Activelle®

2 Qualitative and quantitative composition
Each tablet contains: Estradiol hemihydrate corresponding to estradiol 1 mg, and norethisterone acetate 0,5 mg.

Excipients with known effect:
Contains sugar: Each tablet contains 37 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 Pharmaceutical form
Tablets
White, film-coated, round, biconvex tablets without a dividing score, engraved with NOVO 288 on the one side and the Apis bull on the other side.

4 Clinical particulars
4.1 Therapeutic indications
- Activelle® is indicated for the treatment of vasomotor symptoms associated with estrogen deficiency in women with an intact uterus one year after the menopause.
- To reduce the risk of bone loss in postmenopausal women.

Experience of treating women older than 65 years is limited.
Activelle® has no contraceptive effect.

4.2 Posology and method of administration:
One tablet should be taken orally once a day without interruption, preferably at the same time of the day.
Treatment with Activelle® should preferably be initiated not earlier than one year after the menopause.

In women with amenorrhoea and not taking hormone replacement therapy (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 menopausal symptom relief is not satisfactory after three months, a switch to a higher dose combination product is recommended.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next twelve 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.

Instructions for use of the calendar dial pack
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.

4.3 Contraindications

- Pregnancy or suspected pregnancy
- Lactation
- Known, suspected or past history (personal and/or family) of tumours of the breast, ovary, uterus and liver
- Known or suspected estrogen-dependent malignant tumours (e.g., endometrial cancer)
- Undiagnosed genital bleeding
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism), thromboembolic disorders or stroke or history of these
- Inherited thrombophilia or known thrombophilic disorders (e.g., protein C, protein S or antithrombin deficiency (see section 4.4)
- Active or recent arterial thromboembolic disease (e.g., angina, myocardial infarction)
- Active liver disease. Acute or chronic liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Known hypersensitivity to estradiol, norethisterone acetate or any of the other ingredients of Activelle® (see section 6.1)
- Sickle cell anaemia
- Jaundice or persistent itching during a previous pregnancy
- Endometriosis
- Severe diabetes mellitus with vascular changes
- Disturbances of lipo-metabolism
- Otosclerosis with deterioration during pregnancy
- History of herpes during pregnancy
- Porphyria
- Patients with known inherited genetic mutations: BRCA1 and BRCA2 genes
- Early menstrual periods (before the age of 12 years)
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma *in situ*)
- Previous treatment using radiation therapy to the chest or breast
- Previous exposure to diethylstilbestrol (DES)
- Depression not well controlled with treatment
- A history of depression with the use of estrogen and/or progesterone/progestagen-containing medicines irrespective of the indication, dosage formulation and route of administration.

4.4 Special warnings and precautions for use

Hormone replacement therapy (HRT) (estrogen or estrogen plus a progestin) has been associated with increased risks of certain cancers and cardiovascular diseases, including myocardial infarction and stroke.

HRT should not be initiated or continued to prevent coronary heart diseases.
The benefits and risks of HRT must always be carefully weighed, including consideration of emergence of risks as therapy continues, in particular when considering long-term use.

For the treatment of postmenopausal symptoms, Activelle® 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.

Endometrial hyperplasia and cancer
The risk of endometrial hyperplasia and carcinoma is increased when estrogens, as contained in Activelle®, are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2- to 12- fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see section 4.8). After stopping treatment, the risk may remain elevated for more than 10 years.

The addition of a progestagen, as contained in Activelle®, cyclically for at least 12 days per month/28-day cycle or continuous combined estrogen-progestagen therapy in non-hysterectomised women greatly reduces this risk associated with estrogen-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 on Activelle®, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1 000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65.

Breast cancer
Hormone replacement therapy, including Activelle®, contains estrogen and progestagen which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55 575 women 40 – 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for estrogen-progestagen than estrogen-only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for estrogen-progestagen preparations was 1,60 at 1 – 4 years and RR = 2,08 at 5 – 14 years, while that for estrogen-only preparations were 1,17 at 1 – 4 years and 1,33 at 5 – 14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age.

All women on Activelle® should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.
HRT, such as Activelle®, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism
HRT such as Activelle® 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 three-fold higher risk for users compared with non-users. The occurrence of such an event is more likely in the first year of HRT use than later (see section 4.8).

In women with risk factors for venous thromboembolism (VTE), the benefits of treatment with Activelle® need to be carefully weighed against risks. 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 estrogens, older age, major surgery, prolonged immobilisation, pregnancy/postpartum period, a personal history or family history, severe obesity (body mass index (BMI) > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative 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.

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 portion 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 (see section 4.3).
Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
If VTE develops after initiating therapy, Activelle® 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 estrogen-progestagen or estrogen-only HRT.

The relative risk of CAD during use of combined estrogen-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 estrogen-progestagen use is very low in healthy women close to menopause but will rise with more advanced age.

Stroke
Combined estrogen-progestagen and estrogen-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).

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 estrogen-only or combined estrogen-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).

Medical examination/follow-up
Before initiating or re-instituting Activelle®, a complete personal and family medical history should be taken, together with a thorough general breast and gynaecological examination (including a Pap smear). During treatment regular check-ups are recommended. Women

should be advised what changes in their breasts should be reported to their doctor or nurse. 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.

Regular breast examination and, where appropriate, mammography should be carried out in women on Activelle®. Breast status should also be closely monitored in women with a history of or known breast nodules or fibrocystic disease.

Conditions which need supervision
A careful appraisal of the risk/benefit ratio should be undertaken over time in women treated with Activelle® therapy. If any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment, the benefits of treatment should be weighed against the possible risks. In these cases the patient should be closely supervised. These conditions may recur or be aggravated during treatment with Activelle® (see section 4.3):

- Estrogen-dependent tumours of the breast, uterus, ovaries and liver.
- Leiomyoma (uterine fibroids), endometriosis, or a history of hyperplasia of the endometrium
- Fibrocystic disease of the breast and first-degree relatives of patients with breast cancer
- Thromboembolic disorders or the presence of risk factors
- Hypertension
- Diabetes mellitus with or without vascular involvement
- Liver disorders (e.g. liver adenoma)
- Cholelithiasis
- Otosclerosis which has deteriorated during pregnancy
- Migraine or (severe) headache
- Systemic lupus erythematosus
- Epilepsy
- Multiple sclerosis
- Disturbed liver and renal function
- Heart failure
- Porphyria.

Reasons for immediate withdrawal of Activelle® therapy:
Activelle® 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

Other conditions
Estrogens may cause fluid retention and, therefore, patients with cardiac or renal dysfunction should be carefully observed. Patients with end-stage renal disease should be closely monitored as it would be expected that the circulating levels of the active components of Activelle® would be increased.

In case of aggravation of asthma, epilepsy, or diabetes mellitus, Activelle® should be reconsidered.

It has been reported that there is an increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving estrogens, such as contained in Activelle®.

An increased risk of developing systemic lupus erythematosus during HRT has been reported.

The use of estrogen, as contained in Activelle® may influence the results of certain endocrine and liver function tests.

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

Estrogens 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 estrogen-only HRT after the age of 65.

Depressed mood, depression and risk of suicidality
Mood changes and depression are side effects reported with the use of hormone-containing products including Activelle®. There is some evidence that use of estrogen and/or progesterone/progestagen-containing medicines may be associated with severe depression and a higher risk of suicidal thoughts/behaviour (e.g., talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with Activelle®.

Lactose monohydrate
Activelle® contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take Activelle®.

4.5 Interaction with other medicines and other forms of interaction
The metabolism of the active ingredients in Activelle® may be increased by concomitant use of substances known to induce medicine-metabolising enzymes, specifically cytochrome P450 enzymes such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and decrease the efficiency of Activelle®.

Ritonavir, telaprevir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones, including estradiol and norethisterone acetate. Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of estrogens and progestagens.

Clinically, an increased metabolism of estradiol and norethisterone acetate may lead to decreased effect and changes in the uterine bleeding profile.
Medicines that inhibit the activity of hepatic microsomal medicine-metabolising enzymes e.g., ketoconazole, may increase circulating levels of the active substances in Activelle®.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Activelle® is contraindicated 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 oral contraceptive (OC) and HRT formulations, masculinisation of female foetuses was observed.

Lactation

Activelle® should not be used during lactation.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequently reported side effect 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.

If, following six months of treatment, vaginal bleeding is unacceptable, treatment should be discontinued. If vaginal bleeding persists after the treatment is discontinued, the aetiology of the bleeding should be investigated (see section 4.4).

All side effects 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	**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		
Immune system disorders			Hypersensitivity	
Metabolism and nutrition disorders		Fluid retention		
Psychiatric disorders		Depression or depression aggravated	Nervousness	
Nervous system disorders		Headache, migraine or migraine aggravated		
Vascular disorders			Superficial thrombophlebitis	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	
Musculo-skeletal and connective tissue disorders		Back pain	Leg cramps	
Reproductive system and breast disorders	Breast pain or breast tenderness, vaginal haemorrhage	Breast oedema or breast enlargement, uterine fibroids, aggravated or uterine fibroids reoccurrence or uterine fibroids		
General disorders and administration site conditions		Peripheral oedema	Medicine ineffective	
Investigations		Increased body mass		

Post-marketing experience
In addition to the above-mentioned side effects, 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 side effects cannot be determined.

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

Other side effects have been reported in association with estrogen/progestagen treatment:

- Estrogen-dependent neoplasms benign and malignant, e.g., endometrial cancer
- Venous thromboembolism, i.e., deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see section 4.4)
- Severe depression with a higher risk of suicidal thoughts/behaviour and suicide.

Ovarian cancer risk
Use of estrogen-only or combined estrogen-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.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of Activelle® is important. It allows continued monitoring of the benefit/risk balance of Activelle®. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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

5. Pharmacological properties
5.1 Pharmacodynamic properties:
Category and class: A 21.8.2 Progesterones with estrogens.
Pharmacotherapeutic group: Progestagens and estrogens, fixed combinations
ATC code: G03FA01

The estrogen component of Activelle®, 17β-estradiol, substitutes for the loss of estrogen production in menopausal women. The progestagen component of Activelle®, norethisterone acetate, antagonises the estrogen-induced endometrial hyperplasia.

Women's Health Initiative (WHI) study:
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 hormone replacement therapy (HRT) use in current or recent HRT users.

For estrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which > 80 % of HRT use was estrogen-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 estrogen plus progestagen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with estrogens alone.

The MWS reported that, the use of various types of estrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2,00, 95 % CI: 1,88 – 2,12) than use of estrogens 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 estrogen-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 1 000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1 000 current or recent users of HRT, the number of additional cases during the corresponding period will be:
  - For users of estrogen-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 estrogen 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 estrogen-progestagen combined HRT (CEE + MPA) per 10 000 women years.

According to calculations from the trial data, it is estimated that:
- For 1 000 women in the placebo group
  - about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1 000 women who used estrogen + 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).

5.2 Pharmacokinetic properties:
Following oral administration of 17β-estradiol (E_2) in micronised form, rapid absorption from the gastrointestinal tract occurs. It undergoes extensive first-pass metabolism in the liver and other enteric organs.

After single dose administration, E_2 reaches a peak plasma concentration of approximately 35 pg/mL (range 21 – 52 pg/mL) within 5 – 8 hours.

The half-life of E_2 is about 12 – 14 hours. It circulates bound to sex hormone-binding globulin (37 %) and to albumin (61 %), while only approximately 1 – 2 % is unbound. Metabolism of E_2 occurs mainly in the liver and gut but also in target organs and involves the formation of less active or inactive metabolites, including estrone, catecholoestrogens and several estrogen sulphates and glucuronides. Estrogens 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. After single dose administration, NET 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 sex hormone binding globulin (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 glucoronide conjugates.
The pharmacokinetics in the elderly has not been studied.

5.3 Preclinical safety data
The acute toxicity of estrogens 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 estrogens 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 the professional information.

6 Pharmaceutical particulars

6.1 List of excipients

Copovidone (E335),
Glycerol triacetate (E1518),
Hypromellose,
Lactose monohydrate,
Magnesium stearate (E572),
Maize starch, and
Talc (E553b).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months when stored at or below 25 °C.

6.4 Special precautions for storage

Store at or at or below 25 °C
Store in a dry place, protected from light. Do not refrigerate.
Do not use this product after the expiration date marked on the label of the calendar dial pack and/or carton.

6.5 Nature and contents of container

Activelle® is supplied in a calendar dial pack consisting of a base, ring-shaped lid and a centre dial. Each pack contains 28 tablets.

6.6 Special precautions for disposal and other handling

None.

7 Holder of certificate of registration

Novo Nordisk (Pty) Ltd
150 Rivonia Road
10 Marion Street Office Park
Building C1
Sandton
Johannesburg 2196

8 Registration number

33/21.8.2/0532

9 Date of first authorisation

06 February 2001

10 Date of revision of the text

03 March 2022

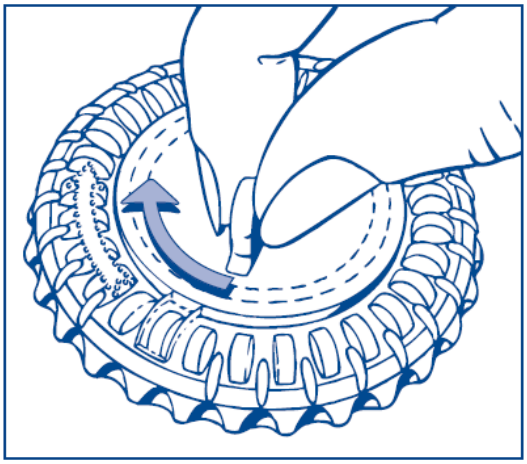
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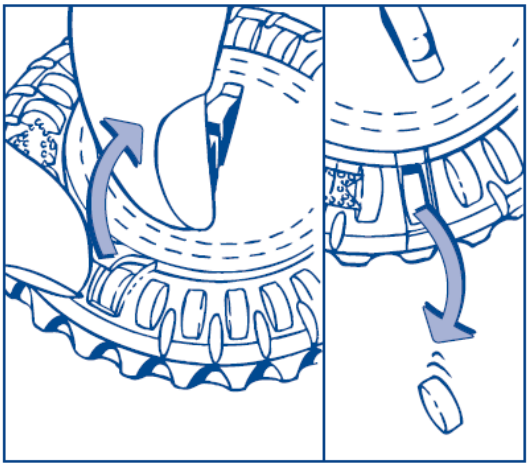
Novo Nordisk A/S

Instructions for use of the calendar dial pack

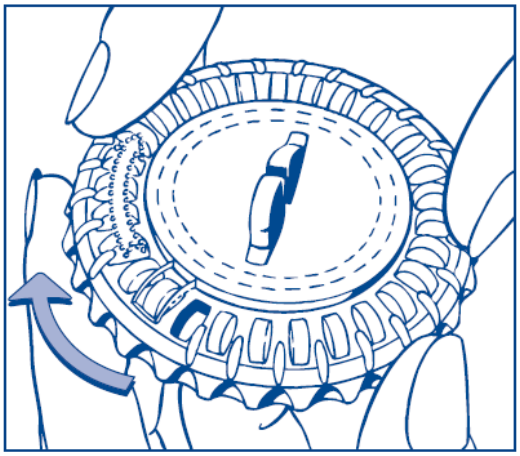
1. Set the day reminder:
Turn the inner disc to set the day of the week opposite the little plastic tab.



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.



Professionele Inligting

S4 Activelle®
Filmbedekte tablette

Skeduleringstatus
S4

1 Naam van die medisyne
Activelle®

2 Kwalitatiewe en kwantitatiewe samestelling
Elke tablet bevat: Estradioolhemihidraat gelykstaande aan estradiool 1 mg en noretisteroonasetaat 0,5 mg.

Bindmiddels met bekende uitwerking:
Bevat suiker: Elke tablet bevat 37 mg laktosemonohidraat.

Sien Afdeling 6.1 vir die volledige lys van bindmiddels.

3 Farmaseutiese vorm
Tablette
Wit, filmbedekte, ronde, bikonvekse tablette sonder ’n verdeelkeep, gegraveer met NOVO 288 aan die een kant en die Apis-bul aan die ander kant.

4 Kliniese besonderhede

4.1 Terapeutiese indikasies
- Activelle® is aangedui vir die behandeling van vasomotoriese simptome wat in verband gebring word met ’n estrogeentekort in vroue met ’n intakte baarmoeder een jaar ná die menopouse.
- Om die risiko van beenverlies in postmenopousale vroue te verlaag.

Ervaring in die behandeling van vroue ouer as 65 jaar is beperk.

Activelle® het geen voorbehoedende uitwerking nie.

4.2 Dosiskunde en metode van toediening:
Een tablet moet ononderbroke een keer per dag mondeliks geneem word, verkieslik op dieselfde tyd van elke dag.

Behandeling met Activelle® moet verkieslik nie vroeër as een jaar ná die menopouse ’n aanvang neem nie.

In vroue met amenoree wat nie hormoonvervangingsterapie (HVT) neem nie, of vroue wat oorskakel van ’n ander deurlopende gekombineerde HVT-produk af, kan behandeling met Activelle® op enige geleë dag begin word. In vroue wat oorskakel van opeenvolgende HVT-regimens af, moet behandeling begin word direk nadat hul onttrekkingsbloeding opgehou het.

As menopousale simptoomverligting ná drie maande nie bevredigend is nie, word ’n oorskakeling na ’n hoërdosiskombinasieproduk aanbeveel.

As die pasiënt vergeet het om ’n tablet te neem, moet die tablet so gou moontlik binne die volgende twaalf ure geneem word. As meer as 12 ure verloop het, moet die tablet

weggegooi word. Om ’n dosis te vergeet, kan die waarskynlikheid van deurbraak- en vlekbloeding vergroot.

Gebruiksaanwysings vir die kalender-draaipak

1. Stel die dag-herinnering:
   Draai die binneste skyfie om die dag van die week regoor die klein plastiekoortjie te stel.

2. Hoe om die eerste tablet te neem:
   Breek die plastiekoortjie af en keer die eerste tablet uit.

3. Elke dag:
   Skuif die deursigtige draaigedeelte bloot kloksgewys met een spasie aan, soos aangedui deur die pyltjie. Keer die volgende tablet uit.

Die deursigtige draaigedeelte kan eers gedraai word nadat die tablet in die opening uitgehaal is.

4.3 Kontra-indikasies

- Swangerskap of vermoedelike swangerskap
- Laktasie
- Bekende, vermoedelike of vorige geskiedenis (persoonlik en/of familie) van gewasse van die borste, eierstokke, baarmoeder en lewer
- Bekende of vermoedelike estrogeen-afhanklike kwaadaardige gewasse (bv. endometriale kanker)
- Ongediagnoseerde genitale bloeding
- Vorige idiopatiese of huidige veneuse trombo-embolisme (diepveneusetrombose, pulmonêre embolisme), trombo-emboliese versteurings of beroerte of geskiedenis hiervan
- Oorgeërfde trombofilie of bekende trombofilieversteurings (bv. proteïen C-, proteïen S- of antitrombientekort (sien Afdeling 4.4)
- Aktiewe of onlangse arteriële trombo-emboliese siekte (bv. angina, miokardiale infarksie)
- Aktiewe lewersiekte. Akute of chroniese lewersiekte of ’n geskiedenis van lewersiekte solank lewerfunksietoetse nie teruggekeer het na normaal toe nie
- Bekende hipersensitiwiteit vir estradiool, noretisteroonasetaat of vir enige van die ander bestanddele van Activelle® (sien Afdeling 6.1).
- Sekelselanemie
- Geelsug of aanhoudende gejeuk tydens ’n vorige swangerskap
- Endometriose
- Erge diabetes mellitus met vaskulêre veranderinge
- Versteurings van lipo-metabolisme
- Otosklerose met agteruitgang tydens swangerskap
- Geskiedenis van herpes tydens swangerskap
- Porfirie
- Pasiënte met bekende oorgeërfde genetiese mutasies: BRCA1- en BRCA2-gene
- Vroeë maandstondes (voor die ouderdom van 12 jaar)
- Geskiedenis van nie-kankeragtige siektes van die borste (atipiese hiperplasie of lobulêre karsinoom *in situ*).
- Vorige behandeling met bestralingsterapie aan die borskas of borste
- Vorige blootstelling aan diëtielstilbestrol (DES)
- Depressie wat nie goed met behandeling beheer word nie
- ’n Geskiedenis van depressie met die gebruik van estrogeen en/of progesteroon/progestogeen-bevattende medisynes, ongeag van die indikasie, doseringsformule en roete van toediening.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Hormoonvervangingsterapie (HVT) (estrogeen of estrogeen plus ’n progestien) is in verband gebring met groter risiko’s van sekere kankers en kardiovaskulêre siektes, met insluiting van miokardiale infarksie en beroerte.

Om koronêre hartsiektes te voorkom, moet HVT nie begin of voortgesit word nie.

Die voordele en risiko’s van HVT moet altyd deeglik opgeweeg word, insluitende die oorweging van die ontstaan van risiko’s namate terapie voortduur, veral wanneer langtermyngebruik oorweeg word.

Vir die behandeling van postmenopousale simptome, moet Activelle® slegs begin word vir simptome wat lewensgehalte nadelig raak. In alle gevalle moet ’n deeglike opweging van die risiko’s en voordele minstens jaarliks gedoen word en HVT moet slegs voortgesit word solank die voordeel swaarder as die risiko weeg.

Bewyse rakende die risiko’s wat verband hou met HVT in die behandeling van premature menopouse, is beperk. Weens die lae vlak van absolute risiko in jonger vroue, kan die balans van voordele en risiko’s vir hierdie vroue dalk meer gunstig wees as in ouer vroue.

Endometriale hiperplasie en kanker
Die risiko van endometriale hiperplasie en karsinoom neem toe wanneer estrogene, soos dié in Activelle®, vir langdurige tydperke op hul eie toegedien word. Die aangemelde groter risiko vir endometriale kanker onder slegs-estrogeen gebruikers varieer tussen 2- en 12-voudig groter in vergelyking met nie-gebruikers, afhangende van die tydsduur van behandeling en die dosis estrogeen (sien Afdeling 4.8). Nadat behandeling gestaak word, kan die risiko vir langer as 10 jaar verhoog bly.

Die toevoeging van ’n progestogeen, soos dié in Activelle®, siklies vir minstens 12 dae per maand/28-dae siklus of deurlopende gekombineerde estrogeen-progestogeenterapie in vroue wat nie ’n histerektomie gehad het nie, verlaag hierdie risiko, wat slegs met estrogeen-HVT in verband gebring word, aansienlik.

Deurbraak- en vlekbloeding kan voorkom tydens die eerste maande van behandeling. As deurbraak- of vlekbloeding ná die eerste maande van behandeling voortduur, na ’n ruk op behandeling met Activelle® verskyn of voortduur nadat behandeling gestaak is, moet die rede ondersoek word, wat ’n endometriale biopsie kan insluit om endometriale kwaadaardigheid uit te skakel.

In vroue met ’n intakte baarmoeder, verhoog die risiko van endometriale hiperplasie en endometriale kanker met toenemende tydsduur van gebruik van onverhinderde estrogene. Luidens data uit epidemiologiese studies, is die beste beraming van die risiko dat vir vroue wat nie HVT gebruik nie, ongeveer 5 uit elke 1 000 na verwagting tussen die ouderdom van 50 en 65 jaar met endometriale kanker gediagnoseer kan word.

Borskanker
Hormoonvervangingsterapie, Activelle® inkluis, bevat estrogeen en progestogeen wat, met langdurige gebruik, die risiko kan vergroot om borskanker te ontwikkel. ’n Meta-ontleding van ondersoekende epidemiologiese studies vanaf 1992 tot 2018 in 55 575 vroue wat 40–59 jaar oud was en menopousale hormoonterapie (MHT) gebruik het, het ’n beduidend groter risiko aangemeld om borskanker te ontwikkel. Die risiko het geleidelik toegeneem met tydsduur van gebruik en was effens groter vir estrogeen-progestogeen- as vir slegs-estrogeenpreparate, en die risiko het vir langer as 10 jaar ná staking van behandeling

voortgeduur. Die relatiewe risiko (RR) om borskanker met estrogeen-progestogeen-preparate te ontwikkel, was 1,60 op 1 – 4 jaar en RR = 2,08 op 5 –14 jaar, terwyl dié vir slegs-estrogeenpreparate 1,17 op 1 – 4 jaar en 1,33 op 5 – 14 jaar was. Daar was geen risiko in vroue wat op 60-jarige ouderdom met MHT begin het, om borskanker te ontwikkel nie.

Alle vroue op Activelle® moet jaarlikse borsondersoeke deur ’n verskaffer van gesondheidsorg ondergaan en hul borste maandeliks self ondersoek. Mammografie-evaluerings moet op grond van die pasiënt se ouderdom, risikofaktore en vorige mammogram-uitslae gedoen word.

HVT, soos Activelle®, vergroot die digtheid van mammografiese beelde, wat die radiologiese opsporing van borskanker kan affekteer.

Veneuse trombo-embolisme
HVT soos Activelle®, word in verband gebring met ’n hoër relatiewe risiko om veneuse trombo-embolisme (VTE) te ontwikkel, d.i. diepveneusetrombose of pulmonêre embolisme. Een gerandomiseerde beheerde proef en epidemiologiese studies het ’n twee- tot drievoudige hoër risiko vir gebruikers in vergelyking met nie-gebruikers bevind. Die voorkoms van so ’n gebeurtenis is meer waarskynlik in die eerste jaar van HVT as later (sien Afdeling 4.8).

In vroue met risikofaktore vir veneuse trombo-embolisme (VTE), moet die voordele van behandeling met Activelle® deeglik teen die risiko’s opgeweeg word. Pasiënte met bekende trombofiliese toestande het ’n groter risiko van VTE en HVT kan bydra tot hierdie risiko. HVT is gevolglik teenaangedui in hierdie pasiënte (sien Afdeling 4.3).

Risikofaktore wat oor die algemeen vir VTE herken word, sluit in die gebruik van estrogene, ouer ouderdom, groot chirurgie, langdurige immobilisering, swangerskap-/nabevallingstydperk, ’n persoonlike of familiegeskiedenis, erge obesiteit (liggaamsmassa-indeks (LMI) > 30 kg/m²) en sistemiese lupus eritematose (SLE). Daar is geen konsensus oor die moontlike rol van spatare in VTE nie.

Die risiko van VTE kan tydelik verhoog met langdurige immobilisering, erge trauma of groot chirurgie. Soos in alle pasiënte wat chirurgie ondergaan het, moet noulettende aandag aan profilaktiese maatreëls geskenk word om VTE ná chirurgie te voorkom. Waar elektiewe chirurgie, veral abdominale chirurgie of ortopediese chirurgie aan die bene, aanleiding sal gee tot langdurige immobilisering, moet oorweging aan die tydelike staking van HVT vier tot ses weke vantevore, indien moontlik, geskenk word. Behandeling moet nie hervat word totdat die vrou heeltemal mobiel is nie.

In vroue met geen persoonlike geskiedenis van VTE nie, maar met ’n eerstegraad bloedverwant met ’n geskiedenis van trombose op ’n jong ouderdom, kan toetsing dalk ná noukeurige berading met betrekking tot die beperkings daarvan (slegs ’n gedeelte van trombofiliese defekte word deur toetsing geïdentifiseer) aangebied word.

Sou ’n trombofiliese defek geïdentifiseer word wat met trombose in familielede segregeer, of as die defek “erg” is (bv. antitrombien-, proteïen S- of proteïen C-tekort of ’n kombinasie van defekte), is HVT teenaangedui (sien Afdeling 4.3).

Vroue wat reeds op chroniese teenstollingsbehandeling is, moet die voordeel-risiko met die gebruik van HVT deeglik opweeg.

As VTE ontwikkel nadat terapie met Activelle® ’n aanvang neem, moet dit gestaak word. Pasiënte moet aangesê word om hul dokters onverwyld te kontak wanneer hulle bewus raak van ’n potensiële trombo-embolitiese simptoom (bv. pynlike swelling van ’n been, skielike pyn in die borskas, dispnee).

Koronêre arteriesiekte (KAS)
Gerandomiseerde beheerde proewe het geen bewys van beskerming teen miokardiale infarksie in vroue met of sonder bestaande KAS wat gekombineerde estrogeen-progestogeen of slegs-estrogeen HVT ontvang het, getoon nie.

Die relatiewe risiko van KAS tydens die gebruik met gekombineerde estrogeen-progestogeen HVT, is effens groter. Aangesien die grondlyn absolute risiko van KAS sterk ouderdomsafhanklik is, is die aantal ekstra gevalle van KAS weens die gebruik van estrogeen-progestogeen in gesonde vroue naby menopouse baie laag, maar sal toeneem met meer gevorderde ouderdom.

Beroerte
Gekombineerde estrogeen-progestogeen- en slegs-estrogeen-terapie is in verband gebring met tot ’n 1,5-voudige groter risiko van isgemiese beroerte. Die relatiewe risiko verander nie met ouderdom of tyd sedert menopouse nie. Aangesien die grondlynrisiko vir beroerte sterk ouderdomsafhanklik is, sal die algehele risiko vir beroerte in vroue wat HVT gebruik egter vergroot met ouderdom (sien Afdeling 4.8).

Kanker van die eierstokke
Kanker van die eierstokke is veel seldsamer as borskanker.

Epidemiologiese bewys uit ’n groot meta-ontleding dui op ’n effens groter risiko in vroue wat slegs-estrogeen- of gekombineerde estrogeen-progestogeen HVT neem, wat binne 5 jaar se gebruik aan die lig kom en oor tyd afneem nadat dit gestaak word.

Ander studies, insluitende die WHI-proef, dui daarop dat die gebruik van gekombineerde HVT’s in verband gebring kan word met ’n eenderse of effens kleiner risiko (sien Afdeling 4.8).

Mediese ondersoek/opvolg
Voordat Activelle® begin of heringestel word, moet ’n volledige persoonlike en familiale mediese geskiedenis geneem word, tesame met ’n deeglike algemene bors- en ginekologiese ondersoek (’n Papsmeer inkluis). Gereelde ondersoeke word tydens behandeling aanbeveel. Vroue moet geadviseer word van watter veranderinge in hul borste by hul dokter of verpleegkundige aangemeld moet word. Ondersoeke, insluitende gepaste beeldnemingsinstrumente, bv. mammografie, moet ooreenkomstig tans-aanvaarde deurligtingspraktyke gedoen en aangepas word vir die kliniese behoeftes van die individu.

Gereelde borsondersoeke en mammografie, waar toepaslik, moet in vroue op Activelle® gedoen word. Borsstatus moet ook noulettend gemonitor word in vroue met ’n geskiedenis van of bekende knoppe in die bors of fibrosistiese siekte.

Toestande wat toesig verg
’n Deeglike opweging van die risiko-/voordeelverhouding moet oor tyd onderneem word in vroue wat met Activelle® terapie behandel word. Sou enige van die volgende toestande teenwoordig wees, voorheen voorgekom het en/of tydens swangerskap of vorige hormoonbehandeling vererger het, moet die voordele van behandeling teen die moontlike risiko’s opgeweeg word. In hierdie gevalle moet die pasiënt onder noulettende toesig wees. Hierdie toestande kan weer opduik of tydens behandeling met Activelle® vererger (sien Afdeling 4.3):

- Estrogeen-afhanklike gewasse van die borste, baarmoeder, eierstokke en lewer
- Leiomioom (uteriene fibroïede), endometriose of ’n geskiedenis van hiperplasie van die endometrium
- Fibrosistiese siekte van die borste en direkte familielede van pasiënte met borskanker
- Trombo-emboliese versteurings of die teenwoordigheid van risikofaktore

- Hipertensie
- Diabetes mellitus, met of sonder vaskulêre betrokkenheid
- Lewerversteurings (bv. leweradenoom)
- Cholelitiase
- Otosklerose wat tydens swangerskap versleg het
- Migraine of (erge) hoofpyn
- Sistemiese lupus eritematose
- Epilepsie
- Veelvuldige sklerose
- Versteurde lewer- en nierfunksie
- Hartversaking
- Porfirie.

Redes vir onmiddellike onttrekking van Activelle® terapie:
Activelle® terapie moet gestaak word as ’n kontra-indikasie aan die lig kom en in die volgende situasies:

- Geelsug of agteruitgang in lewerfunksie
- Beduidende styging in bloeddruk
- Nuwe aanvang van migraine-agtige hoofpyn.
- Swangerskap.

Ander toestande
Estrogene kan vloeistofretensie veroorsaak, gevolglik moet pasiënte met hart- of nierdisfunksie noulettend dopgehou word. Pasiënte met eindstadium niersiekte moet noulettend gemonitor word aangesien daar verwag word dat die sirkulasievlakke van die aktiewe komponente van Activelle® verhoog sal wees.

In geval van verergering van asma, epilepsie of diabetes mellitus, moet Activelle® heroorweeg word.

Daar is aangemeld dat daar ’n groter risiko van chirurgies-bevestigde galblaassiekte in postmenopousale vroue is wat estrogene, soos dié in Activelle®, ontvang.

’n Groter risiko om sistemiese lupus eritematose tydens HVT te ontwikkel, is aangemeld.

Die gebruik van estrogeen, soos dié in Activelle®, kan die uitslae van sekere endokriene en lewerfunksietoetse beïnvloed.

Vroue met voorafbestaande hipertrigliseriedemie moet noulettend tydens estrogeen- of hormoonvervangingsterapie met Activelle® gevolg word, aangesien seldsame gevalle van groot stygings van plasmatrigliseriede, wat aanleiding gee tot pankreatitis, met estrogeenterapie in hierdie toestand aangemeld is.

Estrogene verhoog tiroïedbindingsglobulien (TBG), wat aanleiding gee tot ’n verhoogde sirkulerende totale tiroïedhormoon, soos gemeet deur proteïengebonde jodium (PBI), T4-vlakke (per kolom of per radio-immuunessai) of T3-vlakke (per radio-immuunessai). T3-harsopname neem af, wat die verhoogde TBG reflekteer. Vry T4- en vry T3-konsentrasies is onveranderd. Ander bindingsproteïene kan in serum verhoog wees, d.i. kortikoïed-bindingsglobulien (KBG), geslagshormoonbindingsglobulien (GHBG), wat aanleiding gee tot verhoogde sirkulerende kortikosteroïede en geslagsteroïede, onderskeidelik. Vry of biologies aktiewe hormoonkonsentrasies is onveranderd. Ander plasmaproteïene kan dalk verhoog wees (angiotensienogeen/renien substraat, alpha-I-antitripsien en seruloplasmien).

Gebruik van HVT verbeter nie kognitiewe funksie nie. Daar is wel bewys van ’n groter risiko van moontlike demensie in vroue wat begin om deurlopende gekombineerde of slegs-estrogeen HVT ná die ouderdom van 65 te gebruik.

Risiko van depressiewe gemoed, depressie en selfmoord:
Gemoedsveranderinge en depressie is newe-effekte wat aangemeld is met die gebruik van hormoonbevattende produkte, Activelle® inkluis. Daar is wel bewys dat die gebruik van estrogeen- en/of progesteroon-/progestogeen-bevattende medisynes in verband gebring kan word met erge depressie en ’n hoër risiko van selfmoordgedagtes/-gedrag (bv. praat van selfmoord, onttrek van sosiale kontak, gemoedskommelinge, beheptheid met die dood of geweld, voel hopeloos oor ’n situasie, toenemende gebruik van alkohol/dwelms, doen selfvernietigende goed, persoonlikheidsveranderinge) en selfmoord. Voorskrifskrywers moet vir hul pasiënte sê om hul dokter om advies te kontak as hulle gemoedsveranderinge en depressie ervaar terwyl hulle op behandeling met Activelle® is.

Laktosemonohidraat
Activelle® bevat laktosemonohidraat. Pasiënte met seldsame oorerflike probleme van galaktose-intoleransie, algehele laktosetekort of glukose-galaktose wanabsorpsie, moet nie Activelle® neem nie.

4.5 Interaksie met ander medisynes en ander soorte interaksie
Die metabolisme van die aktiewe bestanddele in Activelle® kan verhoog word deur die samelopende gebruik van middels wat bekend is om medisynemetaboliserende ensieme te induseer, spesifiek sitochroom P450-ensieme, soos stuipwerende middels (bv. fenobarbitaal, fenitoïen, karbaamasepien) en teenbesmettingsmiddels (bv. rifampisien, rifabutien, nevirapien, efavirenz) en verlaag die doeltreffendheid van Activelle®.

Ritonavir, telaprevir en nelfinavir, hoewel dit bekend is as sterk remmers, toon in teenstelling induserende eienskappe wanneer dit samelopend met steroïedhormone gebruik word, estradiool en noretisteroonasetaat inkluis. Kruiepreparate wat Sint Janskruid (*Hypericum perforatum*) bevat, kan die metabolisme van estrogene en progestogene induseer.

Kliniesgesproke, kan ’n verhoogde metabolisme van estradiool en noretisteroonasetaat aanleiding gee tot swakker uitwerking en veranderinge in die baarmoederbloedingsprofiel.

Medisynes wat die werking van hepatiese mikrosomale medisynemetaboliserende ensieme, bv. ketokonasool rem, kan sirkulerende vlakke van die aktiewe stowwe in Activelle® dalk verhoog.

Samelopende toediening van siklosporien en Activelle® kan dalk verhoogde bloedvlakke van siklosporien, kreatinien en transaminases weens laer metabolisme van siklosporien in die lewer veroorsaak.

4.6 Vrugbaarheid, swangerskap en laktasie
Swangerskap.
Activelle® is teenaangedui tydens swangerskap.

As swangerskap tydens medikasie met Activelle® plaasvind, moet behandeling onmiddellik onttrek word.

Data oor ’n beperkte aantal blootgestelde swangerskappe dui op nadelige uitwerkings van noretisteroon op die fetus. Teen dosisse hoër as wat normaalweg in mondelikse voorbehoeding en HVT-formulasies gebruik word, is vermanliking van vroulike fetusse waargeneem.

Laktasie
Activelle® moet nie tydens laktasie gebruik word nie.

Vrugbaarheid
Geen data is beskikbaar nie.

4.7 Uitwerkings op vermoë om te bestuur en masjiene te gebruik
Activelle® het geen bekende uitwerkings op die vermoë om te bestuur of om masjiene te gebruik nie.

4.8 Ongewenste uitwerkings
Die newe-effek wat die gereeldste in die kliniese proewe met Activelle® aangemeld is, was vaginale bloeding en pyn/teerheid van die borste wat in sowat 10 % tot 20 % van pasiënte aangemeld is. Vaginale bloeding het gewoonlik in die eerste maande van behandeling voorgekom. Pyn van die borste het gewoonlik na ’n paar maande se terapie verdwyn.

As vaginale bloeding ná ses maande se behandeling onaanvaarbaar is, moet behandeling gestaak word. As vaginale bloeding voortduur nadat die behandeling gestaak is, moet die etiologie van die bloeding ondersoek word (sien Afdeling 4.4).

Alle newe-effekte wat waargeneem is in die gerandomiseerde kliniese proewe met ’n hoër gereeldheid in pasiënte wat met Activelle® in vergelyking met plasebo behandel is en volgens algehele oordeel dalk verband hou met behandeling, verskyn in die tabel hieronder.

Stelselorgaan	**Baie algemeen** **≥ 1/10**	**Algemeen** **≥ 1/100;** **< 1/10**	**Ongewoon** **≥ 1/1 000;** **< 1/100**	**Seldsaam** **≥ 1/10 000;** **< 1/1 000**
Infeksies en infestasies		Genitale kandidiase of vaginitis		
Versteurings van die immuunstelsel			Hipersensitiwiteit	
Metabolisme- en voedingsverwante versteurings		Vloeistofretensie		
Psigiatriese versteurings		Depressie of verergerde depressie	Senuwee-agtigheid	
Versteurings van die senuweestelsel		Hoofpyn, migraine of verergerde migraine		
Vaskulêre versteurings			Oppervlakkige tromboflebitis	Diep veneuse trombo-embolisme, pulmonêre embolisme
Gastro-intestinale versteurings		Naarheid	Abdominale pyn, abdominale distensie of abdominale ongemak, flatulensie of opgeblasenheid	
Versteurings van die vel en subkutane weefsel			Alopesie, hirsutisme of aknee, pruritus of urtikaria	
Versteurings van die spier-skeletstelsel en bindweefsel		Rugpyn	Beenkrampe	

Versteurings van die voortplantingstelsel en borste	Pyn of teerheid van die borste, vaginale bloeding	Edeem of vergroting van die borste, verergerde uterine fibroïede of hervoorkoms van uterine fibroïede		
Algemene versteurings en toestande by plek van toediening		Perifere edeem	Medisyne is ondoeltreffend	
Ondersoeke		Swaarder liggaamsmassa		

Ná-bemarkingservaring:
Benewens die bogenoemde newe-effekte, is dié wat hieronder genoem word, spontaan aangemeld en word volgens algehele oordeel geag om moontlik verband te hou met behandeling met Activelle®.

Die gereeldheid van aanmelding van hierdie spontane newe-effekte kan nie bepaal word nie:

- Goedaardige en kwaadaardige neoplasmas (siste en poliepe inkluis): kanker van die endometrium
- Versteurings van die immuunstelsel: algemene hipersensitiwiteitsreaksie (bv. anafilaktiese reaksie/skok)
- Psigiatriese versteurings: insomnie, angs, afname in libido, toename in libido
- Versteurings van die senuweestelsel: duiseligheid, beroerte
- Oogversteurings: sigversteurings
- Vaskulêre siektes: verergerde hipertensie
- Gastro-intestinale versteurings: dispepsie, braking
- Versteurings van die lewer en galblaas: galblaassiekte, cholelitiase, verergerde cholelitiase, hervoorkoms van cholelitiase
- Versteurings van die vel en subkutane weefsel: seborree, veluitslag, angio-edeem
- Versteurings van die voortplantingstelsel en borste: endometriale hiperplasie, vulvovaginale pruritus
- Versteurings van die hart: miokardiale infarksie en beroerte
- Ondersoeke: laer liggaamsmassa, hoër bloeddruk.

Ander newe-effekte is aangemeld in verband met estrogeen-/progestogeenbehandeling:

- Estrogeen-afhanklike neoplasmes, goedaardig en kwaadaardig, bv. endometriale kanker
- Veneuse trombo-embolisme, d.i. diepveneusetrombose van die been of bekken en pulmonêre embolisme, kom meer gereeld voor onder gebruikers van hormoonvervangingsterapie as onder nie-gebruikers.
- Versteurings van die vel en subkutane weefsel: chloasma, eriteem multiforme, eriteem nodosum, vaskulêre purpura
- Waarskynlike demensie ouer as 65 (sien Afdeling 4.4)
- Erge depressie met ’n groter risiko van selfmoordgedagtes/-gedrag en selfmoord.

Risiko van kanker van die eierstokke
Gebruik van slegs-estrogeen of gekombineerde estrogeen-progestogeen HVT is in verband gebring met ’n effense groter risiko dat kanker van die eierstokke gediagnoseer word (sien Afdeling 4.4).

’n Meta-ontleding uit 52 epidemiologiese studies het ’n groter risiko vir kanker van die eierstokke aangemeld in vroue wat tans HVT gebruik in vergelyking met vroue wat nog nooit HVT geneem het nie (RR 1,43; 95 % VI 1,31 – 1,56). Vir vroue van 50 tot 54 jaar oud

wat HVT vir 5 jaar neem, het dit sowat 1 ekstra geval per 2 000 gebruikers tot gevolg. In vroue van 50 tot 54 wat nie HVT neem nie, sal sowat 2 vroue uit in 2 000 oor ’n tydperk van 5 jaar met kanker van die eierstokke gediagnoseer word.

Aanmelding van vermoedelike nadelige reaksies:
Die aanmelding van vermoedelike nadelige reaksies ná die magtiging van Activelle® is belangrik. Dit maak voortgesette monitering van die voordeel-/risikobalans van Activelle® moontlik. Verskaffers van gesondheidsorg word gevra om enige vermoedelike nadelige reaksies by SAROG aan te meld aan die hand van die “***6.04 Adverse Drug Reactions Reporting Form***” wat aanlyn onder SAHPRA se publikasies verskyn op: https://www.sahpra.org.za/Publications/Index/8.

4.9 Oordosis
’n Oordosis kan geken word aan naarheid en braking. Behandeling moet simptomaties wees.

5 Farmakologiese eienskappe

5.1 Farmakodinamiese eienskappe:
Kategorie en klas: A 21.8.2 Progesterone met estrogene.

Farmakoterapeutiese groep: Progestogene en estrogene, vaste kombinasies.

ATC-kode: G03FA01

Die estrogeenkomponent van Activelle®, 17β-estradiool, plaasvervangers vir die verlies van estrogeenvervaardiging in menopousale vroue. Die progestogeenkomponent van Activelle®, noretisteroonasetaat, werk die estrogeen-geïnduseerde endometriale hiperplasie tee.

***Women’s Health Initiative*-studie (WHI-studie):**
Borskanker
Volgens bewyse uit ’n groot aantal epidemiologiese studies en een gerandomiseerde plasebobeheerde proef, die WHI, vergroot die algehele risiko van borskanker met verlengde tydsduur van die gebruik van hormoonvervangingsterapie (HVT) in huidige of onlangse HVT-gebruikers.

Vir slegs-estrogeen HVT, is beraamde relatiewe risiko (RR) uit ’n herontleding van oorspronklike data uit 51 epidemiologiese studies (waarin > 80 % van HVT-gebruik slegs estrogeen HVT was) en uit die epidemiologiese *Million Women Study* (MWS) eenders op 1,35 (95 % VI 1,21 – 1,49) en 1,30 (95 % VI 1,21 – 1,40), onderskeidelik.

Vir estrogeen plus progestogeen gekombineerde HVT, het verskeie epidemiologiese studies ’n algehele hoër risiko vir borskanker as met estrogene op hul eie aangemeld.

Die MWS het aangemeld dat die gebruik van verskeie soorte estrogeen-progestogeen gekombineerde HVT in verband gebring is met ’n groter risiko van borskanker (RR = 2,00, 95 % VI: 1,88 – 2,12) as die gebruik van estrogene op hul eie (RR = 1,30, 95 % VI: 1,21 – 1,40) of die gebruik van tibolone (RR = 1,45; 95 % VI 1,25 – 1,68).

Die WHI-proef het ’n beraamde risiko van 1,24 (95 % VI 1,01 – 1,54) ná 5,6 jaar se gebruik van estrogeen-progestogeen gekombineerde HVT (CEE + MPA) in alle gebruikers in vergelyking met plasebo aangemeld.

Die absolute risiko’s wat uit die MWS- en die WHI-proef bereken is, word hieronder voorgehou.

Die MWS het beraam dat, uit die bekende gemiddelde voorkoms van borskanker in ontwikkelde lande:

- word verwag dat sowat 32 uit elke 1 000 vroue wat nie HVT gebruik nie, tussen die ouderdom van 50 en 64 jaar met borskanker gediagnoseer sal word.
- die aantal bykomende gevalle vir 1 000 huidige of onlangse gebruikers van HVT tydens die ooreenstemmende tydperk:
  - vir gebruikers van slegs-estrogeen vervangingsterapie–
    - tussen 0 en 3 (beste beraming = 1,5) vir 5 jaar se gebruik sal wees
    - tussen 3 en 7 (beste beraming = 5) vir 10 jaar se gebruik sal wees.
  - vir gebruikers van estrogeen plus progestogeen gekombineerde HVT–
    - tussen 5 en 7 (beste beraming = 6) vir 5 jaar se gebruik sal wees
    - tussen 18 en 20 (beste beraming = 19) vir 10 jaar se gebruik sal wees.

Die WHI-proef het beraam dat na 5,6 jaar van opvolg van vroue tussen die ouderdom van 50 en 79 jaar, daar 8 bykomende gevalle van indringende borskanker weens estrogeen-progestogeen gekombineerde HVT (CEE + MPA) per 10 000 vrouejare sal wees.

Volgens berekeninge uit die proefdata, word beraam dat:

- vir 1 000 vroue in die plasebogroep–
  - sowat 16 gevalle van indringende borskanker in 5 jaar gediagnoseer sal word.
- vir 1 000 vroue wat estrogeen + progestogeen gekombineerde HVT (CEE + MPA) gebruik het, die aantal bykomende gevalle–
  - tussen 0 en 9 (beste beraming = 4) vir 5 jaar se gebruik sal wees.

Die aantal bykomende gevalle van borskanker in vroue wat HVT gebruik, is oor die algemeen eenders vir vroue wat HVT begin, ongeag van ouderdom met die aanvang van gebruik (tussen die ouderdom van 45 – 65 jaar).

5.2 Farmakokinetiese eienskappe:

Ná mondelikse toediening van 17β-estradiool (E_2) in gemikroniseerde vorm, vind baie vinnige absorpsie uit die spysverteringskanaal plaas. Dit ondergaan uitgebreide eerste-deurgang metabolisme in die lewer en ander ingewandsorgane.

Ná enkeldosistoediening bereik E_2 ’n piekplasmakonsentrasie van ongeveer 35 pg/ml (reeks 21 – 52 pg/ml) binne 5 – 8 ure.

Die halfleeftyd van E_2 is sowat 12 – 14 ure. Dit sirkuleer gebonde aan geslagshormoon-bindingsglobulien (37 %) en aan albumien (61 %), terwyl slegs sowat 1 – 2 % ongebonde is. Metabolisme van E_2 vind hoofsaaklik in die lewer en derm plaas, maar ook in teikenorgane, en behels die vorming van minder aktiewe of onaktiewe metaboliete, insluitende estroon, katesjolestrogene en verskeie estrogeensulfate en glukuroniede. Estrogene word met die gal, waar hulle gehidroliseer en herabsorbeer word (enterohepatiese sirkulasie) en hoofsaaklik in urine in biologies onaktiewe vorm, uitgeskei.

Ná mondelikse toediening word noretisteroonasetaat baie vinnig geabsorbeer en omgeskakel in noretisteroon (NET). Dit ondergaan eerste-deurgang metabolisme in die lewer en ander ingewandsorgane. Ná enkeldosistoediening bereik NET ’n piekplasmakonsentrasie van ongeveer 3,9 ng/ml (reeks 1,4 – 6,8 ng/ml) binne 0,5 – 1,5 uur. Die terminale halfleeftyd van NET is sowat 8 – 11 ure. NET bind aan geslagshormoonbindingsglobulien (36 %) en aan albumien (61 %). Die belangrikste metaboliete is isomere van 5α-dihidro-NET en van tetrahidro-NET, wat hoofsaaklik in die urine uitgeskei word as sulfaat- of glukuroniedkonjugaat.

Die farmakokinetika in bejaardes is nie bestudeer nie.

5.3 Voor-kliniese veiligheidsdata
Estrogene se akute toksisiteit is laag. Weens merkbare verskille tussen dierspesies en tussen diere en mense, het voor-kliniese uitslae ’n beperkte voorspellingswaarde vir die toediening van estrogene in mense.

In proefdiere het estradiool of estradioolvaleraat reeds met betreklik lae dosisse ’n uitwerking getoon wat dodelik vir embrio’s was; misvormings van die urogenitale kanaal en vervrouliking van manlike fetusse is waargeneem.

Noretisteroon, soos ander progestogeen, het vermanliking van vroulike fetusse in rotte en ape veroorsaak. Ná hoë dosisse noretisteroon is uitwerkings waargeneem wat dodelik vir embrio’s was.

Voor-kliniese data wat op konvensionele studies van herhaalde dosistoksisiteit, genotoksisiteit en karsinogeniese potensiaal geskoei is, het geen spesifieke risiko’s vir mense geopenbaar behalwe dié wat in die professionele inligting bespreek is nie.

6 Farmaseutiese besonderhede

6.1 Lys van bindmiddels
Kopovidoon (E335),
Gliseroltriasetaat (E1518);
Hipromellose;
Laktosemonohidraat;
Magnesiumstearaat (E572);
Mieliestysel; en
Talkum (E553b).

6.2 Onverenigbaarhede
Nie van toepassing nie.

6.3 Raklewe
24 maande wanneer dit teen of onder 25 °C bêre word.

6.4 Spesiale voorsorgmaatreëls vir berging
Berg op ’n droë plek, beskerm teen lig. Moenie verkoel nie.

Moenie hierdie produk gebruik ná die vervaldatum wat op die kalender-draaipak en/of die boksie se etikette gemerk is nie.

6.5 Aard en inhoud van houer
Activelle® word voorsien in ’n kalender-draaipak wat bestaan uit ’n basis, ringvormige deksel en ’n middelste draaigedeelte. Elke pakkie bevat 28 tablette.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering
Geen.

7 Houer van Registrasiesertifikaat
Novo Nordisk (Edms.) Bpk.
Rivoniaweg 150
Marionstraat 10 Kantoorpark
Gebou C1
Sandton
Johannesburg, 2196

8 Registrasienommer
33/21.8.2/0532

9 Datum van eerste magtiging
6 Februarie 2001

10 Datum van bywerking van die teks
3 Maart 2022

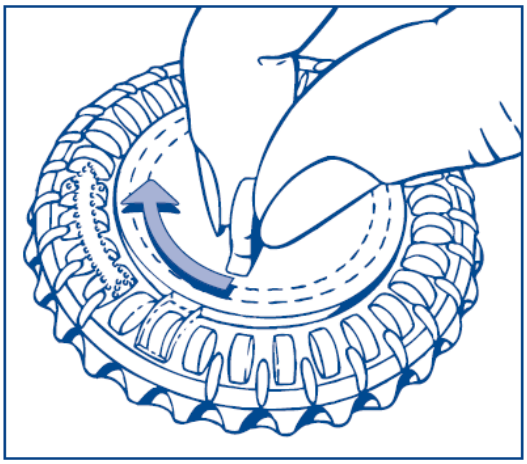
Activelle® is ’n handelsmerk in die besit van Novo Nordisk Health Care AG.

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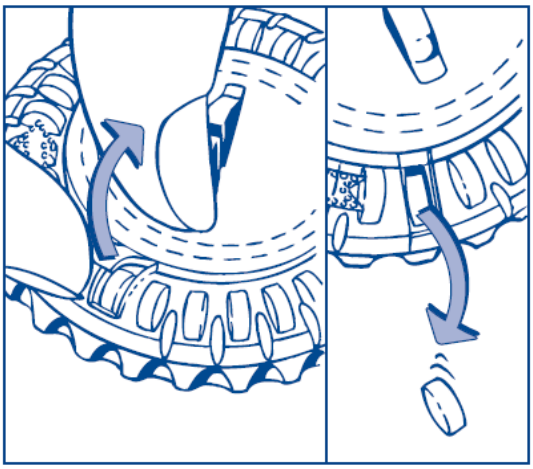
Novo Nordisk A/S

Gebruiksaanwysings vir die kalender-draaipak

1. Stel die dag-herinnering:
Draai die binneste skyfie om die dag van die week regoor die klein plastiekoortjie te stel.



2. Hoe om die eerste tablet te neem:
Breek die plastiekoortjie af en keer die eerste tablet uit.



3. Elke dag:
Skuif die deursigtige draaigedeelte bloot kloksgewys met een spasie aan, soos aangedui deur die pyltjie. Keer die volgende tablet uit.
Die deursigtige draaigedeelte kan eers gedraai word nadat die tablet in die opening uit gehaal is.

