Proposed patient information leaflet for Activelle®

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

Activelle® 1 mg/0,5 mg tablets

Estradiol and norethisterone acetate

Contains sugar: Each tablet contains 37 mg lactose monohydrate.

Read all of this leaflet carefully before you start taking Activelle®

- Keep this leaflet you may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- Activelle® has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What Activelle® is and what it is used for.
2. What you need to know before you take Activelle®.
3. How to take Activelle®.
4. Possible side effects.
5. How to store Activelle®.
6. Contents of the pack and other information.

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1. What Activelle® is and what it is used for

Activelle® is a hormone replacement therapy (HRT). It contains two types of female hormones, an oestrogen and a progestogen, and is used for:

- The treatment of vasomotor symptoms (hot flushes, night sweats) associated with lack of female sex hormones produced by ovaries in women who still have their womb one year after menopause.
- The reduction of the risk of bone loss in postmenopausal women.

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

Activelle® has no contraceptive effect.

2. What you need to know before you take Activelle®

You should not take Activelle® if you:

- Have or suspect you have, or have had breast, ovary, uterus and liver cancer.
- Have a family history of breast cancer.
- Have or suspect you have, a sex hormone-dependent tumour (e.g. cancer of the lining of the womb).
- Have abnormal vaginal bleeding, which has not been diagnosed by your doctor.
- Have or suspect you have or have had deep vein thrombosis (formation of blood clots in the blood vessels of your legs), thromboembolic disorders or pulmonary embolism (formation of blood clots in the blood vessels of your lungs) and stroke.
- Have a blood clotting disorder (such as protein C, protein S or antithrombin deficiency).
- Have or previously have had a disease caused by blood clots in the arteries, such as a heart attack or angina.
- Have an acute or chronic liver disease or a history of liver disease where the liver function tests have failed to return to normal.

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- Are hypersensitive (allergic) to estradiol, norethisterone acetate or any of the other ingredients of Activelle® (see section 6).
- Have sickle cell anaemia (blood disorder characterised by sickle shaped red blood cells).
- Have jaundice (yellow discolouring of the skin and eyes) or persistent itching during a previous pregnancy.
- Have endometriosis (deposition of uterine mucosa outside the womb).
- Have severe diabetes mellitus (high blood sugar) with changes in blood vessels.
- Have lipid metabolism disease.
- Have or have had otosclerosis (a disorder causing deafness in adult life) with deterioration during pregnancy.
- Have had herpes (inflammation of skin or mucous membranes caused by herpes viruses) during pregnancy.
- Have porphyria.
- Are pregnant or suspect you are pregnant.
- Are breastfeeding.
- Have depression, which is not well controlled with treatment.
- Have had depression with previous use of oestrogen and/or progesterone/progestogen-containing medicines.

Before you use Activelle®, tell your doctor if:

- You are known to have inherited genetic changes called BRCA1 and/or BRCA2 genes.
- You started your menstrual periods early (before the age of 12 years).
- You have a history of non-cancerous breast diseases such as atypical hyperplasia or lobular carcinoma *in situ*.
- You had any previous treatment using radiation therapy to the chest or breast.

Sign: 

- You have been treated or exposed while in your mother's womb to a medicine called diethylstilbestrol (DES).

Warnings and precautions

Take special care with Activelle®

Hormone replacement therapy (HRT) (oestrogen or oestrogen plus a progestin) has been associated with increased risks of certain cancers and cardiovascular diseases, including myocardial infarction (heart attack) and stroke.
Activelle® should not be initiated or continued to prevent coronary heart diseases.
The benefits and risks of Activelle® 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 the quality of life.

Tell your doctor if you have or have had the following conditions and/or they have been aggravated during pregnancy or previous hormone treatment.
These conditions may recur or be aggravated during treatment with Activelle®:

- Leiomyoma (benign tumours of the womb), hyperplasia of the endometrium (excessive growth of the womb lining).
- Fibrocystic disease (benign tumour) of your breast.
- High blood pressure.
- High blood sugar (without changes in blood vessels).
- Liver disorders such as a benign liver tumour.
- Cholelithiasis (formation of stones in your gallbladder).
- Migraine or severe headache.

Sign: _____

- You have a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE).
- Epilepsy (fits).
- Multiple sclerosis (chronic disease of the nervous system).
- Disturbed liver and kidney function or end-stage renal disease.
- Heart failure.
- You have high cholesterol (high levels of fat in your body).
- You are on treatment for depression.
- You have had depression with previous use of oestrogen and/or progesterone/progestogen-containing medicines.
- You have a substance abuse problem.
- You have an underlying psychiatric disorder such as post-traumatic stress disorder or bipolar disorder.
- You have a family history of mental disorders.
- You have a history of physical or sexual abuse.

Oestrogen and/or progesterone/progestogen containing medicines, including Activelle®, may cause mood changes and depression, which may be severe. Severe depression is associated with 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.

Stop taking Activelle® (reasons for immediate withdrawal of treatment)

If you are experiencing any of the following conditions below, stop taking Activelle®, and contact your doctor immediately:

- Yellowing of your skin or eyes (jaundice) or other liver problems. These may be signs of a liver disease.
- A large rise in your blood pressure while you are taking Activelle® (symptoms of high blood pressure include headache, tiredness and dizziness).
- A migraine-type headache for the first time (with or without disturbed vision).
- You become pregnant.
- If you experience mood changes and depression contact your doctor for advice.
- You notice signs of a blood clot, such as painful swelling and redness in your legs, sudden chest pain or difficulty in breathing.

In women with risk factors for venous thromboembolism (VTE), the benefits of treatment with Activelle® need to be carefully weighed against risks.

Activelle® and breast cancer

Breast cancer has been diagnosed slightly more often in women who use HRT than in women of the same age who do not use HRT. This slight increase in the number of breast cancer diagnoses gradually disappears during the course of the 10 years after stopping use of HRT. When you are using Activelle®, you must perform monthly breast self-examinations. Your doctor will advise you on when to report for breast examinations and any appropriate investigations.

Endometrial cancer and endometrial hyperplasia

In women with an intact uterus, the risk of excessive growth of the womb lining (endometrial

hyperplasia) and cancer of the lining of the womb (endometrial cancer) is increased when oestrogens are administered alone for long periods. Adding a progestogen, such as contained in Activelle®, reduces this risk.

Breakthrough bleeding and spotting may occur during treatment with Activelle®. If breakthrough bleeding or spotting appears after some time on Activelle® therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude cancer.

Ovarian cancer

Long-term (at least 5 years) use of oestrogen plus progestogen HRT's such as Activelle® has been associated with an increased risk of ovarian cancer in epidemiological studies.

Coronary artery disease (CAD)* – heart *disease

There is no evidence from clinical trials of beneficial effects on the risks of cardiovascular disease with Activelle® therapy in the menopause.

Two large clinical trials in women using combined HRT therapy such as Activelle® showed an increased risk of death related to their hearts and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity and mortality. Therefore, it is uncertain whether these findings also extend to Activelle®.

Stroke

There may be a higher chance of having a stroke if you are taking Activelle®.

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Medical examination/follow-up:

Prior to taking Activelle® and at regular intervals thereafter, your doctor will assess if the treatment is suitable for you. This will include a personal and family medical history and physical examinations as appropriate. You should regularly examine your breasts and report changes to your doctor or nurse. Investigations including mammography should be carried out in accordance with currently accepted screening practices taking into account your clinical needs.

There is a risk to develop breast cancer in women who have been using HRT such as Activelle® for more than 5 years compared with women of the same age who have never used HRT. This risk increases with the duration of intake of HRT and returns to normal after approximately five years of having stopped HRT.

If you are concerned about the risk of breast cancer, discuss the risks and benefits of HRT treatment with your doctor.

Regularly check your breasts. See your doctor if you notice any changes such as:

- dimpling of the skin,
- changes in the nipple, or
- any lumps you can see or feel.

Additionally, you are advised to join mammography screening programs when offered to you. For mammogram screening, it is important that you inform the nurse/health care provider who is actually taking the x-ray that you use Activelle®, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

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Venous thromboembolism (VTE) – blood clots in the deep veins

Activelle® is associated with a risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism (formation of blood clot in the blood vessels of the legs or the lungs).

Some patients are already at risk from developing VTE and this might increase by using Activelle®.

If you:

- Have a history of VTE: If you have had a blood clot before, or have had any blood clotting problem that needed treatment with a medicine such as warfarin.
- Use oestrogen-containing medicine.
- Are of an older age.
- Are immobilised for a long time (e.g. confinement to bed, leg in a plaster cast), if you suffer major injuries to your body or if you undergo major surgery.
- Are pregnant or you just had a baby.
- Are severely overweight.
- Suffer from a condition known as systemic lupus erythematous (SLE) – an autoimmune disease.
- You have had a miscarriage.
- Any of your close family has had blood clots.

Please make sure that your doctor is aware, if any of the above conditions apply to you.

It remains unclear if varicose veins play a role in VTE.

If you know that you are going to have an operation that will result in you being immobilised for a long time, particularly surgery affecting the abdomen or legs, please inform your doctor.

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You may be asked to stop taking Activelle® four to six weeks before surgery to reduce the risk of VTE. You should be able to continue with Activelle® once you are fully mobile again. Prophylactic measures to prevent VTE following surgery should be part of post-operative treatment.

If you develop a painful swelling in your legs or sudden chest pain and experience difficulty in breathing, you should stop taking your Activelle® and contact your doctor immediately, as these may be early signs of VTE.
If VTE develops after initiating therapy, you should stop taking Activelle®.

Studies have shown that women receiving HRT have a relatively higher risk of developing VTE. The risk is two to three times higher in women using HRT than in non-users.

Other conditions you should be aware of:

- Activelle® may cause fluid retention, so if you have a cardiac or renal dysfunction you should be carefully observed by your doctor. If you suffer from kidney failure you should be closely observed since it is expected that the levels of circulating active ingredients in Activelle® will be increased.
- If you have asthma, epilepsy, or diabetes mellitus and these conditions have worsened during Activelle® treatment, your need for 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 oestrogens, such as the one contained in Activelle®.

Other medicines and Activelle®

Always tell your health care provider if you are taking any other medicine. (This includes all complementary or traditional medicine.)

The following medicines interfere with the effect of Activelle® and might lead to irregular bleeding:

- Medicines used for epilepsy (such as anticonvulsants, e.g. barbiturates, phenytoin and carbamazepine).
- Anti-infective medicines (such as anti-tuberculosis medicines, e.g. rifampicin, and medicines used for HIV infections, e.g. nevirapine, efavirenz, ritonavir, telaprevir and nelfinavir).
- Herbal products with St John's wort (*Hypericum perforatum*).

Some medicines may increase the effects of Activelle®:

- Medicines containing azole antifungals such as ketoconazole (a fungicide).

Activelle® may have an impact on a concomitant treatment with ciclosporin (medicines used after transplant procedures).

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

Activelle® with food, drink and alcohol

See section 3.

Sign: _____

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking Activelle®.

Do not take Activelle® if you suspect being pregnant, are pregnant or are breastfeeding your baby.

Driving and using machines

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

Activelle® contains lactose monohydrate

Activelle® contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Activelle®.

3. How to take Activelle®

Activelle® has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Always take Activelle® as your doctor has instructed you. You should check with your doctor or pharmacist if you are not sure.

You may start treatment with Activelle® on any convenient day. If you are transferring from another continuous combined HRT product, treatment with Activelle® may be started on any convenient day. However, if you are switching from a sequential hormone replacement therapy product, treatment should start right after your withdrawal bleeding has ended (if not sure ask your doctor).

Activelle® can be taken with or without food and drink.

Take one tablet once a day, at about the same time each day. Take a tablet every day without interruptions. After all 28 tablets of a calendar dial pack have been used, treatment is continued with the next calendar dial pack without interruption.

Do not chew, crush or break the tablet.

Take the tablet with a sufficient quantity of liquid (e.g. one glass of water).

Tell your doctor if you do not experience symptom relief after three months of treatment.

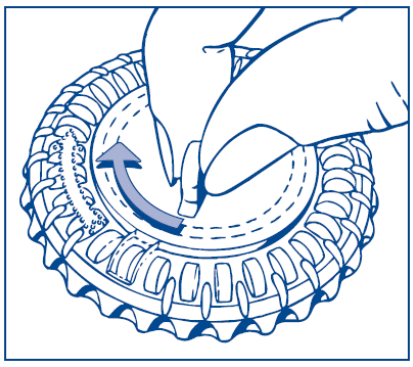
Do not exceed the recommended dosage.

If you have the impression that the effect of Activelle® is too strong or too weak, tell your doctor or pharmacist.

Instructions for use of the calendar pack

1. Set the day reminder.

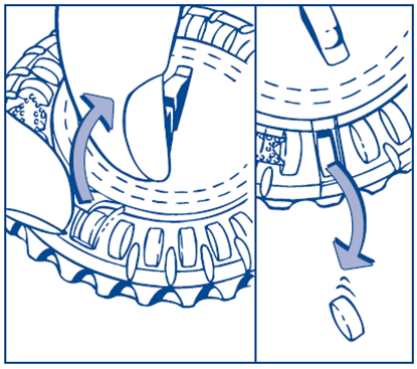
Turn the inner disc to set the day of the week opposite the little plastic tab.



2. How to take the first tablet

Break the plastic tab and tip out the first tablet.

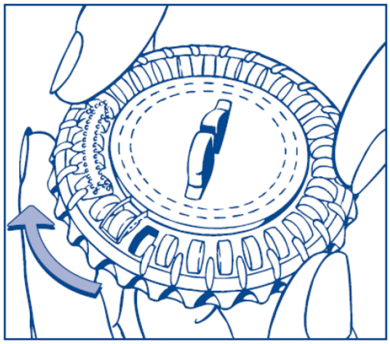
Sign: _____



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.



If you use more Activelle® than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

Overdose of Activelle® could cause nausea and vomiting.

If you forget to take Activelle®

Do not take a double dose to make up for forgotten individual doses.

If you forget to take a tablet, take the tablet as soon as possible within the next twelve hours. If more than 12 hours have passed, discard the tablet and continue treatment as usual. Forgetting a

Sign: _____

dose may increase the likelihood of breakthrough bleeding and spotting if you still have your womb.

If you stop taking Activelle®

If you want to stop taking Activelle®, talk to your doctor first. He/she will explain the effects of stopping treatment and discuss other possibilities with you. If you have any further questions on the use of Activelle®, ask your doctor or pharmacist.

4. Possible side effects

Activelle® can have side effects.

Not all side effects reported for Activelle® are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking Activelle®, please consult your health care provider for advice.

The most frequently reported side effects with Activelle® are vaginal bleeding and breast pain/tenderness. Vaginal bleeding usually occurs in the first months of treatment. Breast pain may disappear after a few months therapy. If following six months of treatment vaginal bleeding is unacceptable, treatment should be discontinued.
Inform your doctor if vaginal bleeding persists after the treatment is discontinued, your doctor will investigate the cause of bleeding.

If any of the following happens, stop taking Activelle® and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Swelling of your hands, feet, ankles, face, lips, tongue,
  mouth or throat, which may cause difficulty in swallowing or breathing; low blood pressure (paleness and coldness of skin, rapid heartbeat), feeling dizzy, sweating.

Sign: 

- Rash or itching.
- Fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Activelle®. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

Frequent:

- Headache, migraine or deterioration of migraine.

Less frequent:

- Superficial inflammation of veins associated with thrombosis (blood clot).
- Pulmonary embolism (blood clot in your lungs causing difficulty breathing).
- Deep venous thromboembolism (blood clots in the leg causing swelling and pain).

The following side effects have been reported but the frequency is unknown:

- Myocardial infarction (heart attack – death of segment of heart muscle), angina and stroke.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent:

- Breast pain or breast tenderness.
- Vaginal bleeding.
- Vaginal thrush with fungus or vaginal inflammation.
- Fluid retention (swelling of the legs, hands or feet).
- Depression or deterioration of depression.
- Nausea (feeling sick).

Sign: 

- Back pain.
- Breast tension or breast enlargement.
- Uterine fibroids (benign tumour of the womb) or

  aggravation or re-occurrence of uterine fibroids.
- Peripheral oedema (swelling of arms or legs).
- Weight increase.

Less frequent:

- Nervousness.
- Abdominal pain, distension or discomfort.
- Flatulence or bloating.
- Hair loss, hirsutism (excessive facial or body hair) or acne.
- Hives.
- Leg cramps.
- Medicine ineffective.

The following side effects have been reported but the frequency is unknown:

- Endometrial cancer (cancer of the lining of the womb).
- Insomnia.
- Anxiety.
- Increased or decreased sexual drive (libido).
- Dizziness.
- Visual disturbances.
- Aggravated high blood pressure.
- Indigestion.
- Vomiting (being sick).
- Gallbladder disease, gallstones, deterioration or re-occurrence of gallstones.
- Greasiness of the skin on your face (seborrhoea).

Sign: _____

- Endometrial hyperplasia (excessive growth of the lining of the womb).
- Vaginal and genital itching.
- Weight decrease.
- Increase in blood pressure.

The following side effects have been seen in women treated with active ingredients (sex hormones: oestrogen/progestogen) similar to the two ingredients in Activelle®:

- Oestrogen-dependent cancer, e.g. endometrial cancer.
- Venous thromboembolism (blood clot in leg vein or pelvic vein and artery conveying blood from the heart to the lungs).
- Chloasma (brown patches on the cheeks or elsewhere on the face).
- Erythema multiforme (skin eruptions which can take various forms).
- Erythema nodosum (skin eruption characterised by tender, bruise-like swellings).
- Vascular purpura (skin rash resulting from bleeding into the skin from small blood vessels).
- Probable dementia (brain disorder) in patients over the age of 65.
- Suicidal thoughts/behaviour and suicide.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8.

By reporting side effects, you can help provide more information on the safety of Activelle®.

Sign: 

5. How to store Activelle®

Store at or below 25 °C.

Store Activelle® in a dry place, protected from light.

Do not refrigerate.

Keep the container in the outer carton until required for use.

Do not use Activelle® after the expiry date stated on the label of the calendar dial pack and outer carton.

Keep all medicine out of the reach of children.

Disposing of Activelle®

Return all unused and or expired Activelle® to your nearest

pharmacy.

Do not dispose of unused medicine in drains and sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What Activelle® contains

Activelle® contains the female sex hormones 17β-estradiol and norethisterone acetate.

Other ingredients are:

Copovidone (E335), glycerol triacetate (E1518), hypromellose, lactose monohydrate, magnesium stearate (E572), maize starch, and talc (E553b).

What Activelle® looks like and contents of the pack

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.

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

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Holder of certificate of registration

Novo Nordisk (Pty) Ltd

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