PATIENT INFORMATION LEAFLET

S4 Kliogest®
Film-coated tablets

SCHEDULING STATUS
S4

Kliogest® film-coated tablets
Estradiol/Norethisterone acetate
Contains sugar: Each tablet contains 36,3 mg lactose monohydrate.

Read all of this leaflet carefully before you start taking Kliogest®
- 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.
- Kliogest® 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 Kliogest® is and what it is used for
Kliogest® is hormone replacement therapy (HRT) used for:
- Hormone replacement in women who are more than one year postmenopausal and still have their wombs.
- The reduction of the risk of bone loss in postmenopausal women.

Kliogest® has no contraceptive effect.

2. What you need to know before you take Kliogest®
If any of the following applies to you, or if you are not sure about any of the points below, talk to your doctor before taking Kliogest®.

Do not take Kliogest®:
- If you have, have had or suspect you have breast cancer.
- If you have a family history of breast cancer.
- If you have, have had or suspect having any estrogen-dependent cancer, e.g. of the womb lining (endometrial cancer), ovarian cancer or any other hormone-dependent cancer.
- If you have any abnormal vaginal bleeding.
- If you have excessive thickening of the womb lining (endometrial hyperplasia).
- If you have endometriosis (a deposition of uterine mucosa outside the womb).
- If you have or have ever had a blood clot in a vein (venous thromboembolism), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism).
- If you have or previously have had a disease caused by blood clots in the arteries, such as a heart attack, stroke or angina.
- If you suffer from any heart disease (cardiovascular disease).
- If you have or have ever had a liver disease and your liver function tests have not returned to normal.
- If you have or have ever had a liver tumour.
- If you have high blood pressure.
- If you are hypersensitive (allergic) to estradiol, norethisterone acetate or any of the ingredients of Kliogest® (see section 6).
- If you have a blood clotting disorder (such as protein C, protein S or antithrombin deficiency).

- If you have a rare blood problem called porphyria which is passed down in families (inherited).
- If you are pregnant.
- If you are breastfeeding.
- If you have depression, which is not well controlled with treatment.
- If you had depression with previous use of estrogen and/or progesterone/progestagen-containing medicines.

Before you use Kliogest®, 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.
- 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 Kliogest®:
Tell your doctor if you have or have had the following conditions as your doctor may want to follow you more closely. These conditions may recur or worsen during treatment with Kliogest® tablets:
- Fibroids inside your womb.
- A history of excessive growth of the womb lining (endometrial hyperplasia).
- Increased risk of getting an estrogen-sensitive cancer (such as having a mother, sister or grandmother who has had endometrial cancer).
- Diabetes mellitus (high blood sugar) (with or without the involvement of blood vessels).
- Gallstones.
- A disease affecting the eardrum and hearing (otosclerosis).
- Migraine or severe headaches.
- Epilepsy (seizures).
- Asthma.
- Heart failure.
- A disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE).
- High cholesterol, a very high level of fat (triglycerides) in your blood.
- Fluid retention due to cardiac or kidney problems.
- You are taking medicine for an underactive thyroid gland – your doctor will perform tests while you are taking Kliogest® to ensure that your thyroid hormone level remains acceptable.
- You have a hereditary condition causing recurrent episodes of severe swelling (hereditary angioedema) or if you have had episodes of rapid swelling of the hands, face, feet, lips, eyes, tongue, throat (airway blockage) or digestive tract.
- You are on treatment for depression.
- You have had depression with previous use of estrogen and/or progesterone/progestagen-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.

Estrogen and/or progesterone/progestagen-containing medicines, including Kliogest®, 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 Kliogest® and see a doctor immediately:
If you notice any of the following when taking Kliogest®:
- Any of the conditions mentioned in the *Do not take Kliogest®* section.
- Yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease.
- A large rise in your blood pressure (symptoms may be headache, tiredness, dizziness).
- Migraine-like headaches which happen for the first time.
- Sudden visual disturbances (changes in your eyesight).
- If you become pregnant.
- If you experience mood changes and depression contact your doctor for advice.
- If you notice signs of a blood clot, such as:
  - painful swelling and redness of the legs.
  - sudden chest pain.
  - difficulty in breathing.

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

Medical history and regular check-ups:
The use of HRT carries risks which need to be considered when deciding whether to start taking it or whether to carry on taking it.
Prior to taking Kliogest® and at 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.
Go for regular breast screening, as recommended by 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 Kliogest®, 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.

Kliogest® and cancer
Endometrial hyperplasia (excessive growth of the lining of the womb) and cancer of the lining of the womb (endometrial cancer)
Some women experience breakthrough bleeding or spotting during the first few months of treatment. If you have any breakthrough bleeding or spotting that continues for longer than the first few months or starts appearing after some time on therapy or continues even though you have stopped taking your treatment, you must tell your doctor as soon as possible.

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

Ovarian cancer
Long-term use (more than 5 years) of estrogen-only HRT plus progestagen HRT products has been associated with an increased risk of ovarian cancer in some epidemiological studies.

Effects of Kliogest® on your heart and circulation

Blood clots (venous thromboembolism (VTE))

Venous thrombosis (sometimes called deep vein thrombosis or DVT) is an event that occurs when clots of blood are formed in the veins, usually in the calf, causing a red, swollen and often painful leg. These clots might move and travel in the blood, a process called venous thromboembolism (VTE). If a clot gets stuck in the lungs it may cause an obstruction, known as pulmonary embolism, which may cause breathlessness and a sharp pain in the chest and/or collapse or fainting.
It can be severe and even fatal.

Some patients are already at risk from developing VTE and this might increase by using Kliogest®. If you:

- Have a history of VTE: If you have had a blood clot before or have had any blood clotting problem.
- Use estrogen-containing medicine.
- Are of an older age.
- Are pregnant or you just had a baby.
- Are severely overweight.
- Suffer from a condition known as systemic lupus erythematous (SLE) – an autoimmune disease.
- Have cancer.
- 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.
The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. 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. You may be asked to stop taking your HRT for four to six weeks before surgery to reduce the risk of VTE. You should be able to continue with your medicine once you are fully mobile again.

If you develop a painful swelling in your leg or abdomen or sudden chest pain and experience difficulty in breathing, you should stop taking your Kliogest® and contact your doctor immediately, as these may be early signs of VTE.

Heart disease (heart attack)

There is no evidence that HRT will prevent a heart attack. Women over the age of 60 years who use estrogen-progestagen HRT are more likely to develop heart disease than those not taking any HRT.

Stroke

The risk of getting stroke is about 1,5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Other conditions

Estrogens, such as the estradiol in Kliogest®, 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 estrogen replacement or HRT such as Kliogest®, since cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Other medicines and Kliogest®
Always tell your health care provider if you are taking any other medicine. (This includes complementary or traditional medicines.)
Some medicines may interfere with the effect of Kliogest®.
This might lead to irregular bleeding.
- Medicines for epilepsy (such as phenobarbital, phenytoin and carbamazepine).
- Medicines for tuberculosis (such as rifampicin and rifabutin).
- Medicines for HIV infections (such as nevirapine, efavirenz, ritonavir, telaprevir and nelfinavir).
- St John's wort (*Hypericum perforatum*).

Other medicines may increase the effects of Kliogest®:
- Medicines containing ketoconazole or itraconazole (fungicides).

Kliogest® may have an impact on a concomitant treatment with ciclosporin.

Laboratory tests
If you need a blood test, tell your doctor or the laboratory staff that you are taking Kliogest® tablets since estrogen can affect the results of certain tests.
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.

Kliogest® with food, drink and alcohol
See section 3.

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 Kliogest®.
Kliogest® is for use in postmenopausal women only. If you become pregnant, stop taking Kliogest® and contact your doctor.
Do not take Kliogest® if you are pregnant or are breastfeeding your baby.

Driving and using machines
Kliogest® can cause side effects, such as headache or visual disturbances. Do not drive a vehicle, operate machinery, or do anything else that requires your attention until you know how Kliogest® may affect you.

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

3. How to take Kliogest®
Do not share medicines prescribed for you with any other person.
Always take Kliogest® exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are not sure.
You may start treatment with Kliogest® on any convenient day.
If you are transferring from another continuous combined HRT product, treatment with Kliogest® 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).
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.
Take the tablet with a sufficient quantity of liquid (e.g., one glass of water).
The tablet can be taken with or without food and drink.
Talk to your doctor if you do not experience symptom relief after three months of treatment.

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

If you take more Kliogest® than you should
In the event of an overdosage, consult your doctor or pharmacist. If neither is available contact the nearest hospital or poison control centre.
Overdose of Kliogest® could give you breast tenderness, irregular bleeding, nausea, vomiting, depressed mood, tiredness, acne (pimples) or male-like hair growth.

If you forget to take/missed a dose of Kliogest®
Do not take a double dose to make up for forgotten individual doses. If you forget to take a tablet one day, discard the tablet and continue treatment as usual. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

If you stop taking Kliogest®
If you would like to stop taking Kliogest® talk to your doctor first, who will explain the effects of stopping treatment and discuss other possibilities with you.
If you have any further questions on the use of Kliogest®, ask your doctor or pharmacist.

4. Possible side effects

Kliogest® can have side effects.
Not all side effects reported for Kliogest® are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking Kliogest®, please consult your health care provider for advice.
If any of the following happens, stop taking Kliogest® and tell your doctor immediately or go to the casualty department at your nearest hospital:

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

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Kliogest®. 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 present migraine.

Less frequent:

- Superficial inflammation of veins associated with thrombosis (blood clot).
- Blood clots in the blood vessels of the legs or the lungs (deep vein thrombosis, lung embolism).

The following side effects have been reported but the frequency is not known:

- Heart attack 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 candidiasis with fungus or vaginal inflammation.
- Fluid retention (swelling of the legs, hands or feet).
- Abdominal pain, swelling or discomfort.
- Depression or deterioration of present depression.
- Nausea (feeling sick).
- Back pain.

- Leg cramps.
- Breast oedema or breast enlargement.
- Uterine fibroids (benign tumour of the womb) or aggravation, occurrence or recurrence.
- Peripheral oedema (swelling of arms or legs).
- Weight increase.

Less frequent:
- Breast cancer.
- Nervousness.
- Flatulence or bloating.
- Hair loss or hirsutism (excessive facial or body hair) or acne.
- Hives (urticaria).
- Medicine ineffective.
- Abnormal (male pattern) hair growth.

The following side effects have been reported but the frequency is not known:
- Cancer of the lining of the womb (endometrial cancer).
- Excessive growth of the lining of the womb (endometrial hyperplasia).
- Increase in blood pressure or worsening of high blood pressure.
- Gallbladder disease, gallstones occurrence/recurrence or aggravated.
- Excessive secretion of sebum, skin eruption.
- Insomnia, dizziness, anxiety.
- Change in sexual desire.
- Visual disturbances.
- Weight decreased.
- Vomiting.
- Heartburn.
- Vaginal and genital itching.

The following side effects have been seen in women treated with active ingredients (sex hormones: estrogen/progestagen) similar to the two ingredients in Kliogest®:
- 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).
- Yellowing of your skin and eyes (called jaundice).
- Decreased glucose tolerance.
- Decreased tolerance of contact lenses, dry eyes.
- 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 Kliogest®.

5. How to store Kliogest®
Store at or below 25 °C.
Store all medicines out of reach of children.
Do not refrigerate.
Keep the container in the outer carton until required for use.
Do not use Kliogest® after the expiry date which is stated on the label and on the calendar dial pack and outer carton.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g., toilets).

6. Contents of the pack and other information

What Kliogest® contains

The active substances are estradiol and norethisterone acetate.
Each white film-coated tablet contains estradiol hemihydrate equivalent to 2 mg estradiol, and 1 mg norethisterone acetate.
The other ingredients are: hydroxypropylcellulose (E463), hypromellose (E464), lactose monohydrate, maize starch, magnesium stearate (E572), talc (E553b), and triacetin (E1518).

The 17β-estradiol contained in Kliogest® is identical to 17β-estradiol in the ovaries of women and is classified as natural estrogen. Norethisterone acetate is a synthetic progestagen, which acts in a similar manner to progesterone, another important female sex hormone.

What Kliogest® looks like and contents of the pack

White, film-coated, round, biconvex tablets engraved with NOVO 281 on one side. Diameter 6 mm.

Kliogest® is supplied in a calendar dial pack each containing 28 tablets.
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.

Holder of certificate of registration

Novo Nordisk (Pty) Ltd
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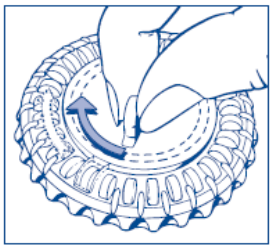
This leaflet was last revised in

Date of registration: 11 March 1996.
Date of text revision: 02 February 2022.

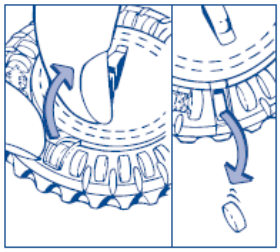
Registration number

Y/21.8.2/230

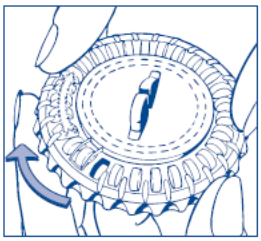
How to use the calendar dial pack



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



2. Take the first day's tablet:
Break the plastic tab and tip out the first tablet.



3. Move the dial every day:
On the next day simply move the transparent dial clockwise one space as indicated by the arrow. Tip out the next tablet.
Remember to take only one tablet once a day.

You can only turn the transparent dial after the tablet in the opening has been removed.