

PATIENT INFORMATION LEAFLET

S4 **Trisequens®**
Film-coated tablets

SCHEDULING STATUS

S4

Trisequens® film-coated tablets

Estradiol/Norethisterone acetate

Contains sugar:

Each blue film-coated tablet contains 36,8 mg lactose monohydrate.

Each white film-coated tablet contains 36,3 mg lactose monohydrate.

Each red film-coated tablet contains 37,3 mg lactose monohydrate.

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

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.

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

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

Trisequens® is hormone replacement therapy (HRT) that is used:

- To relieve unpleasant symptoms of menopause like hot flushes, in postmenopausal women who still have their womb and with at least 6 months since their last natural period.
- As an adjunct therapy in prevention of osteoporosis (thinning of the bones), in postmenopausal women if they are at high risk of future fractures and are unable to take other medicines for this purpose.

Trisequens® has no contraceptive effect.

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

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

If any of the following applies to you. If you are not sure about any of the points below, talk to your doctor before taking Trisequens®.

Do not take Trisequens®:

- If you are pregnant or breastfeeding your baby.
- If you have, have had or suspect you have breast cancer, or you have a family history of breast cancer (mother, sister or grandmother).
- If you have, have had or suspect having any estrogen-dependent cancer, e.g. of the womb lining (endometrial cancer) or any other hormone dependent cancer.
- 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 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 have any abnormal vaginal bleeding.

- If you have excessive thickening of the womb lining (endometrial hyperplasia) that is not being treated.
- If you have porphyria.
- If you have high blood pressure (hypertension).
- If you have a blood clotting disorder (such as protein C, protein S or antithrombin deficiency).
- If you are allergic (hypersensitive) to estradiol, norethisterone acetate or any other ingredients in Trisequens® tablets (see section 6).
- If you have depression, which is not well controlled with treatment.
- If you have had depression with previous use of estrogen and/or progesterone/progestagen-containing medicines.

If any of the above conditions appear for the first time while taking Trisequens®, stop taking it at once and consult your doctor immediately.

Before you use Trisequens®, 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 Trisequens®:

Tell your doctor if you have ever had any of the following problems, before you start treatment with Trisequens®, as these may return or become worse during treatment with Trisequens®. If so, you should see your doctor more often for check-ups (at least once a year):

- Fibroids inside your womb.
- Growth of womb lining outside your womb (endometriosis) or 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 breast and/or endometrial cancer).
- A liver disorder, such as a benign liver tumour, or you have been diagnosed with a liver condition known as Dubin-Johnson syndrome or Rotor syndrome.
- Diabetes mellitus (high blood sugar) (with or without the involvement of blood vessels).
- Gallstones.
- Migraine or severe headaches.
- A disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE).
- Epilepsy.
- Asthma.
- Heart failure.
- A disease affecting the eardrum and hearing (otosclerosis).
- High cholesterol (a very high level of fat in your blood (triglycerides)).
- Fluid retention due to cardiac or kidney problems.
- 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 Trisequens[®], 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 Trisequens[®] and see a doctor immediately:

If you notice any of the following when taking Trisequens[®]:

- Any of the conditions mentioned in the “Do not take Trisequens[®]” section above.
- Yellowing of your skin or the whites of your eyes (jaundice), as these may be signs of a liver disease.
- A large rise in your blood pressure.
- Migraine-like headaches.
- 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.

Note: Trisequens[®] is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

Medical history and regular check-ups

The use of Trisequens[®] carries risks which need to be considered when deciding whether to start taking it or whether to carry on taking it.

Before you start taking Trisequens[®], your doctor will ask about your own and your family's medical history. Your doctor may decide to examine your breasts and/or your abdomen and may do an internal examination. Once you've started on Trisequens[®], you should see your doctor for regular check-ups (at least once a year). At these check-ups, discuss the benefits and risks of continuing to take Trisequens[®] with your doctor.

Go for regular breast screening, as recommended by your doctor.

Effects on your heart or circulation

Heart disease

Trisequens[®] is not recommended for women who have heart disease or have had heart disease recently. If you have ever had heart disease, talk to your doctor to see if you should be taking Trisequens[®].

Trisequens[®] will not help to prevent heart disease.

Woman over the age of 60 years who use estrogen-progestagen HRT, such as Trisequens[®], are more likely to develop heart disease than those not taking any HRT.

If you get:

- A pain in your chest that spreads to your arm or neck.

See a doctor as soon as possible and do not take any more Trisequens[®] until your doctor says you can. This pain could be a sign of heart disease.

Stroke

Recent research suggests that HRT such as Trisequens[®] slightly increases the risk of having a stroke. Other things that can increase the risk of stroke include:

- Getting older.
- High blood pressure.

- Smoking.
- Drinking too much alcohol.
- An irregular heartbeat.

If you are worried about any of these things, or if you have had a stroke in the past, talk to your doctor, to see if you should take Trisequens®.

If you get unexplained migraine-type headaches, with or without disturbed vision, see a doctor as soon as possible and do not take any more Trisequens® until your doctor says you can.

These headaches may be an early warning sign of a stroke.

Blood clots

Trisequens® may increase the risk of blood clots in the veins (also called deep vein thrombosis, or DVT). These blood clots may travel to the lungs and may cause chest pain, breathlessness, collapse or even death. This condition is called pulmonary embolism, or PE.

DVT and PE are examples of a condition called venous thromboembolism, or VTE.

You are more likely to get a blood clot:

- Use estrogen-containing medicine.
- Are of an older age.
- Are pregnant or you just had a baby.
- If you are seriously overweight.
- If you have had a blood clot before.
- If any of your close family have had blood clots.
- If you have had one or more miscarriages.
- If you have any blood clotting problem that needs treatment with a medicine such as warfarin.
- If you're off your feet for a long time because of major surgery, injury or illness.
- Smoking.
- If you have a rare condition called systemic lupus erythematosus (SLE – an autoimmune disease).
- If you have cancer.

If any of the above apply to you, talk to your doctor to see if you should take Trisequens®.

If you're going to have surgery, make sure your doctor knows that you are taking Trisequens®.

You may need to stop taking Trisequens® about 4 to 6 weeks before the operation, to reduce the risk of a blood clot. Ask your doctor when you can start taking Trisequens® again.

Effects on your risk of developing cancer

Breast cancer

Women who have breast cancer, or have had breast cancer in the past, should not take Trisequens®.

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 Trisequens®, you must perform monthly breast self-examinations. Your doctor will advise you on when to report for breast examinations and any appropriate investigations.

See your doctor if you notice any changes such as:

- Dimpling of the skin.
- Changes in the nipple.
- 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 Trisequens®, 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.

Ovarian cancer

Long-term (at least 5 years) use of estrogen-only HRTs and estrogen plus progestagen HRTs, such as Trisequens® is associated with an increased risk of ovarian cancer in some epidemiological studies.

Other conditions

HRT, such as Trisequens®, 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. Consult your health care provider for advice.

Unexpected bleeding

You will have a bleed once a month (so-called withdrawal bleed) while taking Trisequens®. But, if you have unexpected bleeding or drops of blood (spotting) besides your monthly bleeding, which:

- carries on for more than the first 6 months,
- starts after you have been taking Trisequens® more than 6 months,
- carries on after you have stopped taking Trisequens® see your doctor as soon as possible.

Other medicines and Trisequens®

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 Trisequens®. This might lead to irregular bleeding. This applies to the following medicines:

- 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).
- Herbal remedies containing St John's wort (*Hypericum perforatum*).

Other medicines may increase the effects of Trisequens®.

- Medicines containing ketoconazole and itraconazole (fungicides).

Trisequens® 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 Trisequens®, because this medicine can affect the results of some 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.

Trisequens® 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 Trisequens®.

Pregnancy:

Trisequens® is for use in postmenopausal women only. If you become pregnant, stop taking Trisequens® and contact your doctor.

Breastfeeding:

You should not take Trisequens® if you are breastfeeding.

Driving and using machines

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

Trisequens® contains lactose monohydrate

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before Trisequens®.

3. How to take Trisequens®

Do not share medicines prescribed for you with any other person.

Always take Trisequens® exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

If you are not switching from another hormone replacement therapy, you can start treatment with Trisequens® on any convenient day. If you are switching from another hormone replacement therapy, ask your doctor when you should start treatment with Trisequens®.

Take one tablet once a day, at about the same time each day.

Each pack contains 28 tablets.

Days 1 – 12: Take one blue tablet every day for 12 days.

Days 13 – 22: Take one white tablet every day for 10 days.

Days 23 – 28: Take one red tablet every day for 6 days.

Take the tablets with a glass of water.

The tablets can be taken with or without food and drink.

Once you have finished the pack, start a new pack continuing the treatment without interruption.

A menstruation-like bleeding usually occurs at the beginning of a new pack.

For further information on the use of the calendar-dial pack see “**How to use the calendar dial pack**” at the end of the package leaflet.

Speak to your doctor if you think this dose is too strong or not strong enough.

Talk to your doctor if you do not experience symptom relief after 3 months of treatment.

If you take more Trisequens® than you should

If you have taken more Trisequens® than you should, talk to a doctor or a pharmacist. An overdose of Trisequens® could make you feel sick or vomit.

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

If you forget to take the/ missed a dose of Trisequens®

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

If you stop taking Trisequens®

If you would like to stop taking Trisequens® 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 Trisequens®, ask your doctor or pharmacist.

4. Possible side effects

Trisequens® can have side effects.

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

If any of the following happens, stop taking Trisequens® 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 heart beat), 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 Trisequens®. 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 side effects:

- Migraine, new or worse than before.

Less frequent side effects:

- Inflammation of a vein (superficial thrombophlebitis).
- Pulmonary embolism (blood clot).
- Inflammation of a deep vein associated with thrombosis (blood clot).

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 side effects:

- Breast pain or breast tenderness.
- Irregular periods or excessive bleeding during your periods.
- Headache.
- Weight gain.
- Vaginal inflammation.
- Vaginal infection with a fungus.
- Depression, new or worse than before.
- Nausea (feeling sick).
- Abdominal pain, swelling or discomfort.
- Enlargement or swelling of the breasts (breast oedema).
- Back pain.
- Leg cramps.
- Uterine fibroid (benign tumour), aggravation, occurrence or re-occurrence.
- Swelling of arms and legs (peripheral oedema).

Less frequent side effects:

- Bloating or flatulence.
- Acne.
- Hair loss.
- Male pattern hair growth.
- Hives (urticaria).
- Hyperplasia endometrial (excessive growth of the lining of the womb).
- Painful periods.
- Nervousness.
- Cancer of the lining of the womb (endometrial cancer).
- Increase in blood pressure or worsening of high blood pressure.

- Gall bladder disease, gall stones occurrence/recurrence or aggravated.
- Excessive secretion of sebum, skin eruption.
- Insomnia, dizziness, anxiety.
- Change in sexual desire.
- Visual disturbances.
- Decreased body weight.
- Vomiting (being sick).
- Heartburn.
- Vaginal and genital itching.

Other side effects of combined HRT:

The following side effects have also been reported after taking hormone replacement therapy.

- Various skin disorders:
 - discolouration of the skin especially of the face or neck known as 'pregnancy patches' (chloasma).
 - painful reddish skin nodules (erythema nodosum)
 - rash with target-shaped reddening or sores (erythema multiforme).
- 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 Trisequens®.

5. How to store Trisequens®

Store at or below 25 °C. Do not refrigerate.

Store all medicines out of reach of children.

Do not use Trisequens® after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

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

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage system (e.g., toilets).

6. Contents of the pack and other information

What Trisequens® contains

Trisequens® contains two hormones, an estrogen (estradiol) and a progestagen (norethisterone acetate).

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

Each blue film-coated tablet contains: estradiol hemimide equivalent to estradiol 2 mg.

Each white film-coated tablet contains estradiol hemihydrate equivalent to estradiol 2 mg and norethisterone acetate 1 mg.

Each red film-coated tablet contains estradiol hemihydrate equivalent to estradiol 1 mg.

The other ingredients are:
Hydroxypropylcellulose (E463),
Hypromellose (E464),
Lactose monohydrate,
Magnesium stearate (E572),
Maize starch,
Talc (E553b).

Blue film-coated tablets also contain indigo carmine (E132), macrogol 4000 (E1521), and titanium dioxide (E171).

Red film-coated tablets also contain propylene glycol, red iron oxide (E172), and titanium dioxide (E171).

White film-coated tablets also contain triacetin (E1518).

What Trisequens® looks like and contents of the pack

12 Blue film-coated, biconvex tablets engraved with NOVO 280. Diameter 6 mm.
10 White film-coated, biconvex tablets engraved with NOVO 281. Diameter 6 mm.
6 Red film-coated, biconvex tablets engraved with NOVO 282. Diameter 6 mm.

Trisequens® 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

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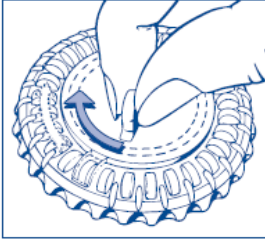
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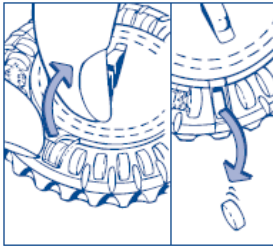
Novo Nordisk A/S

How to use the calendar dial pack



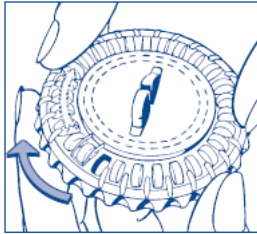
1. Set the day reminder:

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.