PROFESSIONAL INFORMATION

S4 Trisequens®
Film-coated tablets

SCHEDULING STATUS
S4

1 Name of the medicine
Trisequens® film-coated tablets

2 Qualitative and quantitative composition
Each blue film-coated tablet contains: estradiol hemimidrate 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

Excipients with known effect:
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.

For the full list of excipients, see section 6 .1.

3 Pharmaceutical form
Film-coated tablets.

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.

4 Clinical particulars
4.1 Therapeutic indications
Trisequens® is indicated for the treatment of symptoms due to estrogen deficiency, in patients with intact uterus, with at least 6 months since last menses.
Trisequens® therapy may be used as an adjunct in preventing estrogen deficiency related osteoporosis in postmenopausal women with intact uterus.
Trisequens® has no contraceptive effect.
The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration
Trisequens® is a continuous sequential hormone replacement therapy product. The estrogen in Trisequens® is dosed continuously. The progestagen is added for 10 days of every 28 day cycle, in a sequential manner.
The dose is one tablet daily, preferably at the same time each day, until all the 28 tablets have been taken. Treatment should be started by taking the blue tablets (estrogen therapy) for 12 days followed by the white tablets (estrogen/progestagen therapy) for 10 days, and finally the red tablets (estrogen therapy) for 6 days.
After the last red tablet in the pack has been taken, continue treatment the next day by taking the first blue tablet of a new Trisequens® pack. If menstruation is still reasonably regular, the first tablet should be taken on the day immediately after the last day of menstrual bleeding. If there is no menstrual bleeding, or if this occurs only rarely (with intervals of 2 - 4 months) the first tablet can be taken any time.

In women with amenorrhoea and not taking HRT or women with irregular bleeding or women in transition from continuous combined HRT product, treatment with Trisequens® may be started on any convenient day.
In women in transition from another sequential HRT regimen, treatment should begin the day after following completion of the preceding regimen. Women still having periods, should start treatment on the 5th day of withdrawal bleeding.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used. A switch to a higher dose combination product could be indicated if the response after three months is insufficient for satisfactory symptom relief.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used (see section 4.4).

If the patient forgets to take a tablet, the forgotten tablet should be taken as soon as possible within the next 12 hours. If more than 12 hours have passed, the tablet is to be discarded. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

4.3 Contraindications

- Known hypersensitivity to estradiol, norethisterone acetate or to any of the excipients of Trisequens® (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Known, past history (personal and/or family) or suspected breast cancer.
- Known, past or suspected estrogen dependent neoplasia, such as endometrial carcinoma or other hormone dependent tumours.
- Active liver disease. Acute or chronic liver disease or a history of liver disease where the liver function tests have failed to return to normal.
- Venous thromboembolic events or a past history of these conditions i.e., previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).
- Active or previous arterial thromboembolic diseases (e.g., angina, myocardial infarction, stroke).
- Undiagnosed genital bleeding.
- Endometrial hyperplasia.
- Porphyria.
- Hypertension.
- Haemoglobinopathies
- Inherited thrombophilia or known thrombophilic disorders (e.g., protein C, protein S or antithrombin deficiency (see section 4.4).
- Patients known with 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

A careful appraisal of the risks and benefits should be undertaken at least annually and Trisequens® should only be continued as long as the benefit outweighs the risk.
Evidence regarding the risks associated with Trisequens® in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up:
Before initiating or re-instituting Trisequens®, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment periodic check-ups are recommended of a frequency and nature adapted to the individual women. Women should be advised of what changes in their breast should be reported to their doctor. A careful appraisal of the risks and benefits should be undertaken over time in women treated with hormone replacement therapy.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.
Treatment for more than 5 years is not recommended.

Conditions which need supervision:
If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised.
It should be taken into account that these conditions may recur or be aggravated during treatment with Trisequens®:

- Leiomyoma (uterine fibroids) or endometriosis.
- A history of or risk factors for thromboembolic disorders.
- Risk factors for estrogen-dependent tumours, e.g., 1st degree heredity for breast cancer.
- Hypertension.
- Liver disorders (e.g., liver adenoma), Dubin-Johnson syndrome, Rotor syndrome.
- Diabetes mellitus with or without vascular involvement.
- Cholelithiasis.
- Migraine or severe headache.
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia (see section 4.3).
- Epilepsy.
- Asthma.
- Otosclerosis.
- Cardiac failure.

The indications for immediate withdrawal of therapy are as follows:

- Thrombophlebitis, thromboembolic disorders.
- The appearance of jaundice or deterioration in liver function.
- The occurrence of migraine-like headaches.
- Sudden visual disturbances.
- A significant increase in blood pressure.
- Pregnancy.

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

Breast cancer:
Hormone replacement therapy, including Trisequens®, 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 Trisequens® 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, especially estrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism
HRT such as Trisequens® is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include use of estrogens,
older age, major surgery, major trauma, prolonged immobilisation, pregnancy/postpartum period, a personal history or family history, severe obesity (body mass index > 30 kg/m^2) smoking, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE, Trisequens® may add to this risk (see section 4.3). Personal or strong family history of thromboembolism, or recurrent spontaneous abortion, should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of Trisequens® in such patients should be viewed as contraindicated.
If a thrombophilic defect is identified which segregates with VTE 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.
Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of Trisequens®.

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 Trisequens® four to six weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised. If VTE develops after initiating therapy, Trisequens® 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 cardiovascular benefit with continuous combined conjugated estrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS) i.e., Heart and estrogen/progestin Replacement Study) showed an increased risk of cardiovascular morbidity and no overall benefit.

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.

Ovarian cancer:
Ovarian cancer is much rarer than breast cancer.
Epidemiological evidence from a large meta-analysis suggests a lightly 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).

Depressed mood, depression and risk of suicidality:
Mood changes and depression are side effects reported with the use of hormonal containing products including Trisequens®. 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 Trisequens®.

Other conditions:
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 radio-immunoassay) or T3 levels (by radio- Immuno-assay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e., corticoid binding globulins (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-1-antitrypsin and ceruloplasmin).

Estrogen, an ingredient of Trisequens®, may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be
carefully observed.

Patients with severe renal impairment should be closely observed, since it is expected that the level of circulating active ingredients in Trisequens® will increase.

Women with pre-existing hypertriglyceridaemia should be followed closely during Trisequens® therapy, since cases of large increases of plasma triglycerides leading to pancreatitis have been reported.

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.

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

4.5 Interaction with other medicines and other forms of interaction
The metabolism of estrogens and progestagens such as in Trisequens® 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). Ritonavir, telaprevir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St

John's wort (*Hypericum perforatum*) may induce the metabolism of estrogens and progestagens such as in Trisequens®. Clinically, an increased metabolism of estrogens and progestagens as in Trisequens® may lead to decreased effect and changes in the uterine bleeding profile.

Medicines that inhibit the activity of hepatic microsomal medicines metabolising enzymes e.g., ketoconazoles and itraconazole may increase circulating levels of the active substances in Trisequens®

Concomitant administration of ciclosporin 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

Trisequens is contraindicated during pregnancy.
If pregnancy occurs during medication with Trisequens®, treatment should be withdrawn immediately.
Clinically, data on a limited number of exposed pregnancies indicate adverse effects of norethisterone on the fetus. At doses higher than those normally used in OC and HRT formulations, masculinisation of female fetuses was observed.
The results of most epidemiological studies to date, relevant to inadvertent fetal exposure to combinations of estrogens and progestagens, indicate no teratogenic or fetotoxic effect.

Lactation

Trisequens is contraindicated during lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequently reported adverse events in the clinical trials with Trisequens® 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 disappears after few months of therapy.

All adverse events observed in the randomised clinical trials with a higher frequency in patients treated with Trisequens® as compared to placebo and which are possibly related to treatment, are presented in the table below:

System organ class	**Very common ≥ 1/10**	**Common ≥ 1/100 - < 1/10**	**Uncommon ≥ 1/1 000 - < 1/100**	**Rare ≥ 1/10 000 - < 1/1 000**
Infections and infestations		Genital candidiasis or vaginitis (see also "Reproductive system and breast disorders")		
Immune system disorders			Hypersensitivity (see also "Skin and subcutaneous tissue disorders")	
Metabolism and nutrition disorders		Fluid retention (see also "General disorders and administration site conditions")		
Psychiatric disorders		Depression or depression aggravated	Nervousness	

Nervous system disorders		Headache, migraine or migraine aggravated		
Vascular disorders			Superficial thrombophlebitis	Pulmonary embolism, deep thrombophlebitis
Gastrointestinal disorders		Nausea, abdominal pain, abdominal distention or abdominal discomfort	Flatulence or bloating	
Skin and subcutaneous tissue disorders			Alopecia, hirsutism or acne, pruritus or urticaria	
Musculoskeletal and connective tissue disorders		Back pain, leg cramps		
Reproductive system and breast disorders	Breast pain or breast tenderness, irregular menstruation or menorrhagia	Breast oedema or breast enlargement, uterine fibroids aggravated or uterine fibroids recurrence or uterine fibroids	Endometrial hyperplasia, dysmenorrhoea (see also *back pain* under "Musculoskeletal and connective tissue disorders" and *abdominal pain* under "Gastrointestinal disorders")	
General disorders and administration site conditions		Peripheral oedema	Medicine ineffective	
Investigations		Increased body mass		

Post-marketing experience:
In addition to the above-mentioned adverse reactions, those presented below have been spontaneously reported, and are considered possibly related to Trisequens® treatment.

Neoplasms benign and malignant (including cysts and polyps):
Endometrial cancer.
Immune system disorders: Generalised hypersensitivity reactions (e.g., anaphylactic shock).
Psychiatric disorders: Insomnia, anxiety, libido decreased, libido increased.
Nervous disorders: Dizziness, stroke.
Eye disorders: Visual disturbances.
Vascular disorders: Hypertension aggravated.
Cardiac disorders: Myocardial infarction.
Gastrointestinal disorders: Dyspepsia, vomiting.
Hepatobiliary disorders: Gall bladder disease, cholelithiasis, can be aggravated, or can re-occur.
Skin and subcutaneous tissue disorders: Seborrhoea, rash, angioedema.
Reproductive system and breast disorders: Vulvovaginal pruritus.
Investigations: Body mass decreased, blood pressure increased.
Other adverse reactions that have been reported in association with estrogen/progestagen treatment include:

- Skin and subcutaneous tissue disorders: Alopecia, chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Immune system disorders: Generalised hypersensitivity reactions (e.g., anaphylactic reaction/shock).
- Dementia over the age of 65.
- Severe depression with a higher risk of suicidal thoughts/behaviour and suicide.

If any side effects persist or intensify, the patient should consult a doctor.

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 Trisequens® is important. It allows continued monitoring of the benefit/risk balance of Trisequens®. Healthcare 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
Estrogens cause side effects which are related to their estrogenic and general metabolic effects. Overdosage may cause undesirable proliferation of the uterus, sodium and water retention, enlargement of the breasts, headache, dizziness, 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, sequential preparations
ATC code: G03FB05

Estradiol (E_2): The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol.

Norethisterone acetate (NETA) inhibits the effect of estrogen on the endometrium.
Regular withdrawal bleeding occurred in 93 % of women with a mean duration of 3 - 4 days.

5.2 Pharmacokinetic properties
Following oral administration of 17β-estradiol in micronised form, it is well absorbed from the gastrointestinal tract. It undergoes extensive first pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 44 pg/mL (range 30 – 53 pg/mL) within 6 hours after intake of 2 mg. The half-life of 17β-estradiol is about 18 hours. It circulates bound to SHBG (37 %) and to albumin (61 %), while only approximately 1 – 2 % is unbound. Metabolism of 17β-estradiol occurs mainly in the liver and the gut but also in target organs and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several estrogen sulphates and glucuronides. Estrogens are excreted with the bile, hydrolysed and reabsorbed (enterohepatic circulation) mainly eliminated in urine, in biologically inactive forms.

After oral administration, NETA is well absorbed and transformed to norethisterone (NET). It undergoes first pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 9 ng/mL (range 6 – 11 ng/mL) within 1 hour after intake of 1 mg. The terminal half- life of NET is about 10 hours. NET binds to SHBG (36 %) and to albumin (61 %). The most important metabolites are isomers of 5α-dihydro-NET and tetrahydro-NET, which are excreted mainly in the urine as sulphate or glucuronide conjugates.
The pharmacokinetics of estradiol is not influenced by norethisterone acetate.

The pharmacokinetic properties in the elderly have not been studied.

5.3 Preclinical safety data
The toxicity profiles of estradiol and norethisterone acetate are well known. There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the professional information.

6 Pharmaceutical particulars
6.1 List of excipients
Hydroxypropylcellulose (E463),
Hypromellose (E464),
Lactose monohydrate,
Magnesium stearate (E572),
Maize starch,
Talc (E553b).

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

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

White film-coated tablets:
triacetin (E1518).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.
Store at or below 25 °C.

6.4 Special precautions for storage
Do not refrigerate.
Keep the container in the outer carton until required for use.
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.

6.5 Nature and contents of container
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.

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
J/21.8.2/212

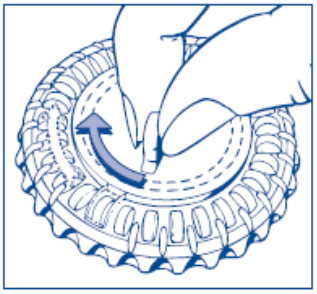
9 Date of first authorisation/renewal of the authorisation
27 August 1979

10 Date of revision of the text
01 February 2022

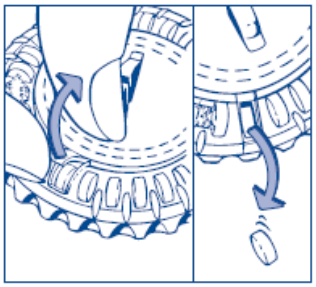
Trisequens® is a trademark owned by Novo Nordisk Health Care AG.

Novo Nordisk A/S

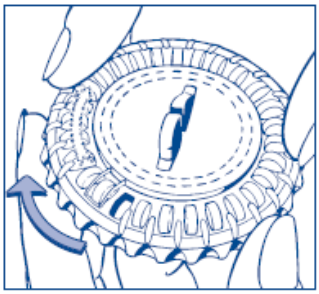
Use of the calendar dial pack



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.