AUSTRALIAN PRODUCT INFORMATION

TRISEQUENS®
estradiol tablets and norethisterone acetate plus estradiol tablets dial dispenser pack.

WARNING

Estrogens and progestagens should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see 'Section 5.1 Pharmacodynamic Properties' - 'Clinical trials' and 'Section 4.4 Special Warnings and Precautions for Use').

The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated estrogens (0.625 mg) relative to placebo (see 'Section 5.1 Pharmacodynamic Properties' - 'Clinical trials' and 'Section 4.4 Special Warnings and Precautions for Use').

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated estrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (see 'Section 5.1 Pharmacodynamic Properties' - 'Clinical trials' and 'Section 4.4 Special Warnings and Precautions for Use').

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestagens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestagens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1. NAME OF THE MEDICINE

Estradiol hemihydrate and norethisterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trisequens is a sequential estrogen/progestagen hormone replacement therapy (HRT) preparation formulated with the natural human estrogen, estradiol, and norethisterone acetate. The first 12 tablets in the calendar dial pack contain estradiol alone. In the next 10 tablets norethisterone acetate is added to induce endometrial shedding. The last 6 tablets contain a low dose of estradiol. This regimen provides adequate estrogen replacement throughout the

cycle and reduces the risk of endometrial hyperplasia. The composition of the tablets is shown in Table 1 below.

Table 1

	Trisequens		
Colour of tablets	blue	white	red
Number of tablets per Calendar pack	12	10	6
Estradiol (as hemihydrate) (micronised)	2.0 mg	2.0 mg	1.0 mg
Norethisterone Acetate (micronised)	-	1.0 mg	-

Excipient with known effect: lactose monohydrate. For the full list of excipients, see 'Section 6.1 List of excipients.'

3. PHARMACEUTICAL FORM

Film coated tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short term symptomatic treatment of estrogen deficiency associated with natural or artificial menopause (see 'Section 4.2 Dose and Method of Administration' and 'Section 5.1 Pharmacodynamic Properties' - 'Clinical trials').

4.2 Dose and Method of Administration

Dosage

Trisequens is a continuous sequential HRT product. The estrogen is dosed continuously. The progestagen is added for 10 days of every 28 day cycle, in a sequential manner.

In menstruating women treatment with Trisequens should be started on the fifth day of menstrual bleeding. All other patients may start at any time.

Regular withdrawal bleeding will be established, usually during the administration of the red low-estrogen tablets, or possibly even during the last phase of the white tablets.

If symptoms such as hot flushes have ceased, consideration of transferring to local vaginal treatment should be given if troublesome local symptoms remain.

Duration of therapy

HRT should be prescribed at the lowest effective dose and for shortest duration (see 'Section 4.4 Special Warnings and Precautions for Use'). The continuation of the treatment should be re-evaluated annually. Women who have undergone a premature menopause may require longer term treatment.

Method of Administration

Trisequens is administered orally one tablet daily without interruption. Treatment should begin with the administration of the blue tablets (2mg estradiol) for 12 days, followed by the

white tablets (2 mg estradiol, 1 mg norethisterone acetate) for 10 days, and then the red tablets (1 mg estradiol) for 6 days. When all the 28 tablets in the pack have been taken, another pack is started.

If the patient has forgotten to take a tablet, the tablet is to be discarded. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

Use of the calendar pack
The first tablet to be taken is under the sealed opening in the transparent outer rim of the pack. Turn the inner disc of the pack until the day of the week on which the first tablet is to be taken is opposite the sealed opening. The seal is then lifted off with a finger nail and the first tablet removed from the pack. Each day turn the transparent outer rim of the pack in the direction of the arrow to obtain the next tablet. Continue until all tablets have been taken.

4.3 Contraindications

- Known, suspected, or past history of carcinoma of the breast
- Known, suspected or past history of estrogen dependent neoplasia e.g. endometrial carcinoma
- Untreated endometrial hyperplasia
- Genital bleeding of unknown aetiology
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency (see 'Section 4.4 Special Warnings and Precautions for Use'))
- Active or previous arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria
- Known hypersensitivity to the active ingredients or any of the excipients
- Known or suspected pregnancy.

4.4 Special Warnings and Precautions for Use

HRT should not be initiated or continued to prevent or treat cardiovascular disease.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. A careful appraisal of the risks and benefits should be undertaken at least annually.

HRT should be used only in women with menopausal symptoms and ordinarily not for long term use. HRT should be prescribed at the lowest effective doses and for the shortest duration consistent with the treatment goals and risks for the individual women.

Trisequens tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

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 Product Information.

Medical examination/follow-up
Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examinations should be guided by this and by the contraindications and warnings for use.

There is a need for caution when prescribing estrogens in women with known or past history of breast nodules or fibrocystic disease or family history of breast cancer and in women with established coronary artery disease.

During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman including gynaecological examinations.

Women should be advised what changes in their breasts should be reported to their doctor or nurse (see the "Breast cancer" section below). Investigations including appropriate imaging tools e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

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

Reasons for immediate withdrawal of therapy
Therapy should be discontinued in case a contraindication is discovered or in the following situations:
- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy
- Sudden visual disturbance.

Venous thromboembolism
HRT is associated with a 1.3- to 3-fold risk of developing venous thromboembolism (VTE), i.e. deep venous thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see 'Section 4.8 Adverse Effects (Undesirable

Effects)'). The risk versus the benefits should therefore be carefully weighed in consultation with the individual woman when prescribing HRT to women with a risk factor for VTE.

Patients with known thrombophilic states have an increased risk of VTE, and HRT may add to this risk. HRT is therefore contraindicated in these patients (see 'Section 4.3 Contraindications'). Generally recognised risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), use of estrogens, major surgery, prolonged immobilisation, pregnancy/postpartum period, systemic lupus erythematosus (SLE), obesity, and cancer. The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

The risk of VTE may be temporarily increased with prolonged immobilisation, major elective or post-traumatic surgery or major trauma. Depending on the nature of the event and the duration of the immobilisation, consideration should be given to a temporary discontinuation of HRT. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of VTE at a young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members, or if the defect is 'severe' (e.g. antithrombin, protein S or protein C deficiencies, or a combination of defects), HRT is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of using HRT.

If VTE develops after initiating therapy, the drug 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).

Scarabin and others[(4)] reported the results of a case control study conducted during 1999-2002 in France. The investigators recruited 155 consecutive cases with a first documented episode of VTE of unknown cause (92 with pulmonary embolisms and 63 with deep venous thrombosis), and 381 controls (women admitted to hospital for other reasons) matched for centre, age, and time of recruitment. Overall, 32 (21%) cases and 27 (7%) controls were current users of oral estrogen replacement therapy (this was defined in this study as estrogen only therapy or combined HRT), whereas 30 (19%) cases and 93 (24%) controls were current users of transdermal estrogen replacement therapy. After adjustment for potential confounding variables, the odds ratio for VTE in current users of oral and transdermal estrogen replacement therapy compared with non-users was 3.5 (95% CI 1.8-6.8) and 0.9 (0.5-1.6), respectively. Estimated risk for VTE in current users of oral estrogen replacement therapy compared with transdermal estrogen replacement therapy users was 4.0 (1.9-8.3). These results may be interpreted as meaning that (i) the higher risk of VTE as shown in the WHI study has been further supported; and (ii) current use but not past use was a risk factor

for VTE. Use in the first year was also more risky than later use, a finding that is also consistent with the WHI study.

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 a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke
One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Endometrial hyperplasia and carcinoma
There is some evidence that obesity and possibly hypertension or diabetes mellitus, are predisposing factors to endometrial carcinoma. Patients with these conditions and those with a family history of endometrial carcinoma should be monitored closely.

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

The addition of a progestagen for at least 10 days per cycle in non-hysterectomised women greatly reduces this risk. Patients who are, or have previously been, treated with unopposed estrogens should be examined with special care to exclude endometrial stimulation before commencing Trisequens therapy.

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
The use of estrogen-only and combined estrogen-progestagen by women has been shown to increase the risk of breast cancer, that is dependent on the duration of taking HRT.

Combined estrogen-progestagen therapy:
The randomised placebo-controlled trial, the Women’s Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased

risk of breast cancer in women taking combined estrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see 'Section 4.8 Adverse Effects (Undesirable Effects)').

Estrogen only therapy:
The WHI trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of estrogen-progestagen combinations (see 'Section 4.8 Adverse Effects (Undesirable Effects)').

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

Women using estrogen-progestagen combined HRT had a higher risk as compared with women who used estrogens alone. Although obese women are at an increased risk of having breast cancer, HRT did not further increase this risk.
A randomised clinical trial (WHI study) with conjugated estrogens and MPA showed that the risk of breast cancer increases with the number of years of HRT usage and gets significant in year 5 of HRT use. The absolute increase in risk is small to moderate (see '5.1 Pharmacodynamic Properties' - 'Clinical trials'). The Million Women Study demonstrated that this risk increase is similar for different estrogen-progestagen combinations, different regimens and routes of hormone administration. Whether the low dose HRT has a different effect on breast cancer risk is still unclear.
In the WHI study, the continuous combined conjugated equine estrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. The use of estrogen plus progestagen has been reported to result in an increase in abnormal mammograms requiring further evaluation. Mammographic density may be increased after the use of combined HRT. This may have implications for the sensitivity and specificity of breast cancer screening. Regular breast examination and, where appropriate, mammography should be carried out in women on HRT. Breast status should also be closely monitored in women with a history of or known breast nodules, fibrocystic disease, or with a family history of breast cancer.

Combination HRT should not be used in hysterectomised women because it is not needed in these women and it may increase the risk of breast cancer.

<u>Ovarian cancer</u>
Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies,

including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see 'Section 4.8 Adverse Effects (Undesirable Effects)').

Dementia
See 'Section 5.1 Pharmacodynamic Properties' - 'Clinical trials' (WHIMS sub-study). HRT use does not improve cognitive function.

Other conditions
It is advisable to withdraw treatment 4 to 6 weeks before major surgery.

Pre-existing uterine fibromyoma may increase in size with estrogens. If this is observed, estrogen therapy should be discontinued.

Trisequens has no contraceptive effect.

The risks and benefits in younger women receiving treatment for the short-term management of menopausal symptoms of estrogen deficiency or for the management of premature menopause were not examined in the WHI study. As well, the study did not include other formulations or dosage regimens, such as Novo Nordisk's products containing 17-beta-estradiol and norethisterone acetate, or other routes of administration of HRT.

In the absence of data specific to this product, if prescribing any form of hormone replacement therapy as primary prevention of osteoporosis, the potential for increased cardiovascular, thrombotic and neoplastic adverse events must be considered. Combined hormone replacement therapy should not be used for the long-term maintenance of general health, including the primary prevention of cardiovascular disease. Estrogen or estrogenic compounds must not be used alone as estrogen replacement therapy in women who have not had a hysterectomy.

Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Trisequens will increase.

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

Patients who require thyroid hormone replacement therapy should have their thyroid function monitored regularly while on HRT to ensure that thyroid hormone levels remain in an acceptable range. 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-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

Estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

Use in elderly
The experience of treating women older than 65 years' is limited. Pharmacokinetics in the elderly have not been studied.

Of the total number of subjects in the conjugated equine estrogens in combination with medroxyprogesterone acetate sub-study of the Women's Health Initiative study[(1)], 44% (n = 7,320) were 65 years and over, while 6.6% (n = 1,095) were 75 and over. No significant differences in overall safety were observed between subjects 65 years and over compared to younger subjects. There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to younger subjects.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed up for an average of 4 years, 82% were 65-74 (3,726) while 18% (806) were 75 and over. Most women (80%) had no prior HRT use. Women treated with 0.625 mg conjugated estrogens, plus 2.5 mg medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Ninety percent of cases of probable dementia occurred in the 54% of women that were older than 70.

Paediatric use
No data available.

Effects on laboratory tests
Some laboratory tests may be influenced by estrogen therapy, such as tests for glucose tolerance or thyroid function.

4.5 Interaction with Other Medicines and Other Form of Interactions

The metabolism of estrogens and progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes such as barbiturates (e.g. phenobarbital), anticonvulsants (e.g. phenytoin, carbamazepin), antihistamines, phenylbutazone and some anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz, telaprevir). 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.

Clinically, an increased metabolism of estrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Reduced estradiol levels have been observed under the simultaneous use of antibiotics e.g. penicillins and tetracycline.

Drugs that inhibit the activity of hepatic microsomal drug metabolising enzymes e.g. ketoconazole, may increase circulating levels of the active substances in Trisequens.

Estrogens can also affect the actions of other drugs e.g. anticoagulants, antidiabetic agents, antifibrinolytic agents, pethidine, drugs which decrease serum folate, imipramine, thyroid hormones and corticosteroids.

Oral contraceptives (OC) containing ethinylestradiol have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered. Similar interaction may exist between HRT containing estradiol and lamotrigine. Therefore, dosage adjustment of lamotrigine may be necessary for seizure control.

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

4.6 Fertility, Pregnancy and Lactation

Effects on fertility
No data available.

Use in pregnancy
Contraindicated (Category D). If pregnancy occurs during medication with Trisequens, treatment should be withdrawn immediately.

In animal studies, maternal administration of high doses of estrogens has produced urogenital malformations in the offspring. The relevance of these animal findings for the clinical use of estradiol is uncertain, but is considered likely to be low. Animal studies have also shown that high doses of progestagens can cause masculinisation of the female foetus.

Clinically, data on a limited number of pregnancies indicate adverse effects of norethisterone on the fetus. At doses higher than 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.

Use in lactation
Trisequens is not indicated during lactation.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Clinical experience
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 disappeared after a few months of therapy. All adverse events observed in the randomised clinical trials with a higher frequency in patients treated with Trisequens or similar HRT products as compared to placebo and which on an overall judgement are possibly related to treatment are presented in the table below, see also ‘Section 5.1 Pharmacodynamic Properties’ - ‘Clinical trials’ and ‘Section 4.4 Special Warnings and Precautions for Use’.

Table 2

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <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			Thrombophlebitis superficial	Pulmonary embolism Thrombophlebitis deep
Gastrointestinal disorders		Nausea Abdominal pain, abdominal distension or abdominal discomfort	Flatulence or bloating	
Skin and subcutaneous tissue disorders			Alopecia, hirsutism or acne Pruritus or urticaria	
Musculoskeletal, connective tissue and bone disorders		Back pain Leg cramps		
Reproductive system and breast disorders	Breast pain or breast tenderness Menstruation irregular or menorrhagia	Breast oedema or breast enlargement Uterine fibroids aggravated or uterine fibroids reoccurrence or uterine fibroids	Endometrial hyperplasia Dysmenorrhoea (see also *back pain* under *Musculoskeletal, connective tissue and bone disorders* and *abdominal*	

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
			pain under *Gastrointestinal disorders*)	
General disorders and administration site conditions		Oedema peripheral	Drug ineffective	
Investigations		Weight increased		

Endometrial cancer
In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to estrogen-only therapy greatly reduces this increased risk.

Post-marketing experience
In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgment considered possibly related to Trisequens treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (<1/10,000, not known (cannot be estimated from the available data)). Post-marketing experience is subject to underreporting especially with regard to trivial and well known adverse drug reactions. The presented frequencies should be interpreted in that light:

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

The following adverse reactions have been reported in association with estrogen/progestagen treatment:
- Skin and subcutaneous disorders: alopecia, chloasma, erythema multiforme, erythema nodosum, vascular purpura

- Probable dementia (see 'Section 4.4 Special Warnings and Precautions for Use')
- Gastrointestinal disorders: Crohn's disease, ulcerative colitis
- Dry eyes
- Tear film composition changes.

Breast cancer risk
An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestagen therapy for more than 5 years. The increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestagen combinations. The level of risk is dependent on the duration of use (see 'Section 4.4 Special Warnings and Precautions for Use').

Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented below.

Table 3 Largest Meta-analysis of prospective epidemiological studies – Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at starting HRT (years)	**Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)***	**Risk ratio**	**Additional cases per 1000 HRT users after 5 years'**
Estrogen-only HRT			
50	13.3	1.2	2.7
Combined estrogen-progestagen			
50	13.3	1.6	8.0
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m²). Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

Table 4 Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m²)

Age at starting HRT (years)	**Incidence per 1,000 never users of HRT over a 10 year period (50-59 years)***	**Risk ratio**	**Additional cases per 1,000 HRT users after 10 years**
Estrogen-only HRT			
50	26.6	1.3	7.1
Combined estrogen-progestagen			
50	26.6	1.8	20.8
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m²). Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

Table 5 US WHI studies – Additional risk of breast cancer after 5 years' use

Age range (years)	**Incidence per 1000 women in placebo arm over 5 years**	**Risk ratio and 95% CI**	**Additional cases per 1000 HRT users over 5 years' use (95% CI)**
CEE estrogen-only			
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0) *

CEE+MPA estrogen-progestagen**			
50 - 79	17	1.2 (1.0 - 1.5)	4 (0 - 9)
* WHI study in women with no uterus, which did not show an increase in risk of breast cancer **When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment. After 5 years the risk was higher than in non-users.			

Ovarian cancer
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 Special Warnings and Precautions for Use'). 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.

Risk of venous thromboembolism
HRT is associated with a 1.3- to 3-fold increased 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 using HRT (see 'Section 4.4 Special Warnings and Precautions for Use'). Results of the WHI studies are presented below:

Table 6 WHI Studies – Additional risk of VTE over 5 years' use

Age range (years)	**Incidence per 1000 women in placebo arm over 5 years**	**Risk ratio and 95% CI**	**Additional cases per 1000 HRT users over 5 years' use (95% CI)**
Oral estrogen-only*			
50 - 59	7	1.2 (0.6 - 2.4)	1 (-3 – 10)
Oral combined estrogen-progestagen			
50 - 59	4	2.3 (1.2 - 4.3)	5 (1 - 13)
* Study in women with no uterus			

Risk of coronary artery disease
The risk of coronary artery disease is slightly increased in users of combined estrogen-progestagen HRT over the age of 60 (see 'Section 4.4 Special Warnings and Precautions for Use').

Risk of ischaemic stroke
The use of estrogen-only and estrogen-progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see 'Section 4.4 Special Warnings and Precautions for Use').

Table 7 WHI studies combined – Additional risk of ischaemic stroke* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users over 5 years' use (95% CI)
50 - 59	8	1.3 (1.1 – 1.6)	3 (1 – 5)
*No differentiation was made between ischaemic and haemorrhagic stroke			

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose
Overdosage may cause nausea and vomiting, headache, dizziness, endometrial proliferation, sodium and water retention, and breast enlargement. There are no specific recommendations for the management of overdosage.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action
The pharmacological actions of exogenous estradiol are similar to the physiological effects of the endogenous hormone. Norethisterone acetate given orally has progestational actions similar to those of progesterone and, in addition, has weak estrogenic and androgenic properties.

Trisequens restores plasma estrogen levels and thus relieves or decreases subjective estrogen deficiency symptoms. Trisequens therapy has been demonstrated to suppress gonadotrophin secretion (FSH/LH) and to improve vaginal cytology in peri- and post-menopausal women without adversely affecting the serum lipid profile or inducing liver protein synthesis (e.g. various clotting factors).

A regular withdrawal bleeding is established with Trisequens. The addition of norethisterone acetate in the second series of (white) tablets induces a change in the endometrium to a secretory phase. Endometrial shedding usually occurs during the third series of (red) tablets. The low estradiol content in the last series of tablets prevents the reappearance of menopausal symptoms without affecting withdrawal bleeding.

Clinical trials

WHI Study[(1)]
In a prospective randomised trial (Women's Health Initiative, WHI) involving 8506 postmenopausal women who received oral hormone replacement therapy (HRT) using a continuous combined regimen of conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day and 8102 women who received placebo for an average of 5.2 years, adverse effects on cardiovascular disease and breast cancer, and

beneficial effects on hip and total fractures and colorectal cancer were observed. These results do not necessarily apply to lower dosages of these drugs, to other formulations of oral estrogens and progestins, or to estrogen monotherapy.

The WHI study was designed to investigate the efficacy and safety of long-term HRT in preventing coronary heart disease (CHD) in healthy postmenopausal women with an intact uterus. A global index summarising the balance of risks and benefits included an analysis of the 2 primary outcomes, invasive breast cancer and CHD, and the following secondary outcomes: stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. The women enrolled in the study had a mean age at entry of 63.3 years. On average they were overweight (mean body mass index [BMI] = 28.5) and one-third were obese (BMI=≥ 30), 50% were previous or current smokers, one-third had received treatment for high blood pressure and over 10% had raised cholesterol levels requiring medication.

After a mean of 5.2 years of follow up, the study was prematurely stopped because the risk-benefit profile was not consistent with the requirements for a viable intervention for primary prevention of chronic diseases.

Table 8: Increased Risks

	Relative Risk (RR)	Placebo arm: Cases/10000	CEE+MPA arm: Cases/10000	Increased Absolute Risk per 10000 women / year
Breast Cancer	1.26	30	38	8
Stroke	1.41	21	29	8
CHD	1.29	30	37	7
Thromboembolic Events (blood clots in legs and lungs)	2.11	16	34	18

Table 9: Decreased Risks

	Relative Risk (RR)	Placebo arm: Cases/10000	CEE+MPA arm: Cases/10000	Decreased Absolute Risk per 10000 women / year
Colorectal Cancer	0.63	16	10	6
Hip Fractures	0.66	15	10	5
Total Fractures	0.76	191	147	44

Million Women Study[(2)]

The results of the cohort study (see Table 4) were based on the follow up on one million, eighty-four thousand, one hundred and ten (1,084,110) women. The average age of the women at recruitment was 55.9 years and the average period of follow up was 2.6 years for analyses of the cancer incidence and 4.1 years for analyses of mortality; the average duration of treatment was over 6 years. Overall, 50% of the study population had used HRT at some point. There were nine thousand, three hundred and sixty four (9,364) newly diagnosed cases of invasive breast cancer and six hundred and thirty seven (637) deaths from breast cancers. The current users of HRT at recruitment were more likely to be diagnosed with breast cancer and to die from it. Past users of HRT were not at an increased risk of newly diagnosed or fatal

disease. The incidence was significantly increased for current users of preparations containing estrogen only, estrogen/progestagen and tibolone but the magnitude of the associated risk was greater for the combined treatment than for any other preparation.

Table 10: Relative risk of newly diagnosed invasive breast cancer in relation to recency and type of HRT used

HRT use at baseline	*Cases / population*	*Relative risk (95% FCI)**
All never users	2894/392,757	1.00 (0.96-1.04)
All past users	1044/150,179	1.01 (0.95-1.08)
Current users of:		
Estrogen only	991/115,383	1.30 (1.22-1.38)
Estrogen-progestagen	1934/142,870	2.00 (1.91-2.09)
Tibolone	184/18,186	1.45 (1.25-1.67)
Other/unknown types	93/9,548	1.44 (1.17-1.76)

FCI=floated CI. *Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region and deprivation index.
Modified from Lancet 2003; 362:421

An important finding of the Million Women study was that the relative risks of breast cancer were increased separately from oral, transdermal and implanted estrogen only formulations.

In terms of absolute risk, after ten years' use of HRT, it is estimated that there would be 5 (95% CI 3-7) additional breast cancers per 1,000 users of estrogen only preparations and 19 (95% CI 15-23) additional cancers per 1,000 users of estrogen/progestagen combinations. The elevated risk reduces after discontinuation of hormone replacement therapy and is effectively lost after 5 years.

In the combined HRT subset of WHI, a 26% increase of invasive breast cancer (38 versus 30 per 10,000 person years) after an average of 5.2 years treatment was observed in women receiving the estrogen/progestagen combination compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on study medication. Women reporting prior postmenopausal hormone use had a higher relative risk for breast cancer associated with HRT than those who never used postmenopausal hormones.

WHIMS sub-study[3]
In a study of women 65 years of age and older (a randomised controlled sub-study of the Women's Health Initiative, the Women's Health Initiative Memory Study; n = 4,532, 54% older than 70), those treated with 0.625 mg conjugated equine estrogens plus 2.5mg medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. After an average follow-up of 4 years, the absolute risk of probable dementia was 45 per 10,000 women-years in the estrogen plus progestagen group and 22 per 10,000 women-years in the placebo group. It is unknown whether these findings apply to younger postmenopausal women. It is unlikely that HRT would be indicated in this age group.

5.2 Pharmacokinetic Properties

Micronised estradiol is rapidly and efficiently absorbed from the gastrointestinal tract following oral administration. Some estradiol is converted to estrone in the intestinal mucosa before absorption into the portal vein. During passage through the liver a significant proportion of estradiol is metabolised to estrone. Estriol and hydroxyoestrones are also produced as well as sulfate and glucuronate conjugates. Circulating estrone sulfate may be

reconverted to estrone and estradiol in extrahepatic organs like the uterus. Estrogens are partly bound to plasma proteins including sex hormone binding globulin. Estrogens are excreted into the bile and undergo significant enterohepatic cycling. Conjugates of the various estrogens and their metabolites are excreted in the urine and unconjugated estrogen metabolites appear in the faeces. Estrogens are also secreted in the milk of nursing mothers.

Norethisterone acetate is rapidly absorbed and transformed to norethisterone, then metabolised and excreted as glucuronide and sulfate conjugates. About half the dose is recovered in the urine within 24 hours, the remainder being reduced to less than 1% of the dose within 5-6 days. The terminal plasma half life is about 10 hours.

Peak plasma concentrations of estradiol occur 2-4 h after tablet ingestion. Thereafter elimination is slow and estradiol levels are maintained above baseline for 24 h. Peak plasma concentrations of norethisterone occur 1-2 h after tablet ingestion. Norethisterone concentrations return to basal levels within 24 h.

5.3 Preclinical Safety Data

Genotoxicity
There is limited evidence available in the literature suggesting that estradiol may be weakly genotoxic. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy and an increased incidence of sister chromatid exchanges (indicative of DNA damage) in mammalian cells. None of these effects were induced by estradiol in human lymphocyte cultures. Importantly, there was no evidence of clastogenicity in rodent bone marrow micronucleus assays.

Carcinogenicity
Supra-physiological doses of estradiol have been associated with the induction of tumours in estrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
The tablet cores of the blue, white and red tablets contain: lactose monohydrate, maize starch, hyprolose, purified talc, magnesium stearate.

Film-coatings
Blue tablets: hypromellose, purified talc, titanium dioxide (E171), indigo carmine (E132) and macrogol 400.
White tablets: hypromellose, triacetin and purified talc.
Red tablets: hypromellose, purified talc, titanium dioxide (E171), red iron oxide (E172), and propylene glycol.

6.2 Incompatibilities
Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Keep all medicines out of reach of children. Trisequens should be kept in a cool dry place where the temperature stays below 25ºC. Do not store Trisequens in the refrigerator. Keep the container in the outer carton in order to protect it from light.

6.5 Nature and Contents of Container

Trisequens is supplied in a calendar dial pack consisting of a polypropylene base and polystyrene lid containing 28 tablets (12 blue tablets, 10 white tablets and 6 red tablets). See 'Section 2 Qualitative and Quantitative Composition'.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 Physicochemical Properties

Estradiol is a white or almost white crystalline powder which is practically insoluble in water and soluble in acetone.

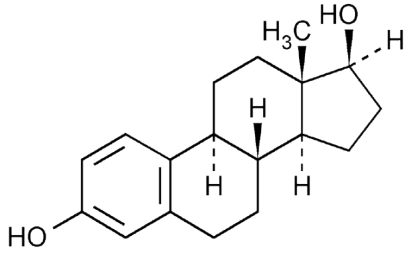
Norethisterone acetate (NETA) is a white or yellowish-white crystalline powder which is practically insoluble in water and soluble in ethanol and acetone.

Chemical structure

Estradiol - chemical name: estra-1,3,5(10)-triene-3,17β-diol (as hemihydrate). Estradiol has 5 chiral centres. The molecular formula is $C_{18}H_{24}O_2$. Estradiol hemihydrate has a molecular weight of 281.39.

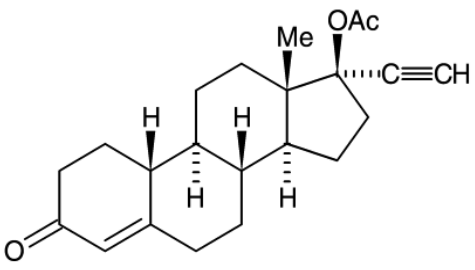
Norethisterone acetate - chemical name: 17β-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one. Norethisterone acetate has 6 chiral centres. The molecular formula is $C_{22}H_{28}O_3$, with a molecular weight of 340.5.

Estradiol hemihydrate



'½H_2O'

Norethisterone acetate



CAS number
Estradiol hemihydrate: 35380-71-3
Norethisterone acetate: 51-98-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Ltd
Level 10, 118 Mount Street
North Sydney NSW 2060

9. DATE OF FIRST APPROVAL

11 January 2012

10. DATE OF REVISION

8 January 2024

REFERENCES

(1) Writing Group for the Women's Health Initiative. JAMA 2002; 288:321-333
(2) Million Women Study Collaborators. Lancet 2003; 362:419-427
(3) Shumaker SA, Legault C, et al. JAMA 2003; 289:2651-2662
(4) Scarabin P-Y, Oger E, et al. Lancet 2003; 362:428-432

Summary table of changes

Section changed	Summary of new information
4.8	Updated terminology for angioedema