New Zealand Data Sheet

1 PRODUCT NAME

SANDRENA, estradiol (as hemihydrate) 0.1%, gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SANDRENA gel contains estradiol 1 mg/g.

Each 0.5 g sachet of gel contains 0.5 mg of estradiol (as hemihydrate).

Each 1 g sachet of gel contains 1 mg of estradiol (as hemihydrate).

Excipient with known effect:

One gram of gel contains 125 mg propylene glycol and 585 mg ethanol (96%).

For the full list of excipients, see *section 6.1 List of excipients*.

3 PHARMACEUTICAL FORM

Gel, single dose container.

The product is a smooth opalescent gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the climacteric syndrome associated with natural or artificial menopause (oestrogen deficiency symptoms, eg hot flushes, night sweats and urogenital atrophy).

Prevention of postmenopausal osteoporosis.

4.2 Dose and method of administration

SANDRENA is a gel for transdermal use. SANDRENA can be used for continuous, cyclic or sequential treatment.

The usual starting dose is 1.0 mg estradiol (1,0 g gel) daily but the selection of the initial dose can be based on the severity of the patients' symptoms. Depending on the clinical response, the dosage can be readjusted after 2 to 3 cycles individually from 0.5 g to 1.5 g per day, corresponding to 0.5 to 1.5 mg estradiol per day.

In patients with an intact uterus, it is necessary to combine SANDRENA with an adequate dose of progestin for adequate duration, at least 12–14 consecutive days per month/28 day cycle to oppose oestrogen-stimulated hyperplasia of the endometrium.

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestin in hysterectomised women.

Method of administration

Apply on dry and clean skin.

The SANDRENA dose is applied once daily, on the skin of the lower trunk or the thigh. The application surface should be 1-2 times the size of the hand. SANDRENA should not be applied on the breasts, on the face or irritated skin. After application the gel should be allowed to dry for a few minutes and the application site should not be washed for one hour. Contact of the gel with the eyes should be avoided.

- Hands should be washed with soap and water after application
- As soon as the gel has dried after application, the application site should be covered

with clothing

- Application site should be showered before situations where skin contact with others is expected
- If another person (e.g. child or spouse) or pet accidentally touches the application site, that area of their skin should be washed with soap and water right away.

If no precautionary measures are taken, the estradiol gel can be accidentally transferred through close skin contact to others (e.g. child, spouse, pets), which may cause adverse effects to them. In case of any signs of symptoms of adverse effects, physician or veterinarian should be contacted.

Patients should be informed that children should not come in contact with the area of the body where estradiol gel was applied on (see *section 4.4 Special warnings and precautions for use*).

In women who are not using hormone replacement therapy (HRT), or women transferring from continuous combined HRT-product, treatment with SANDRENA may be started on any convenient day. In women transferring from a sequential or cyclic HRT regimen, treatment should begin the day following completion of the prior 28 days regimen.

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

If the patient has forgotten to apply one dose, the forgotten dose is to be applied as soon as possible if the dose is not more than 12 hours late. If the dose is more than 12 hours late the dose should be forgotten and continue as normal. Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

Improvement of symptoms generally occurs within a few weeks, but optimal results are obtained when therapy is continued for at least 3 months. SANDRENA should be prescribed for the shortest duration consistent with treatment goals. Review the need for continuation of treatment after 6 months, taking into account the risk-benefit ratio for the individual user at that moment.

4.3 Contraindications

- Undiagnosed genital bleeding.
- Active or recent arterial thromboembolic diseases (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function has failed to return to normal
- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Untreated endometrial hyperplasia
- 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*)
- Porphyria
- Hypersensitivity to the active substance or to any of the excipients listed in *section 6.1 List of excipients*.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits

should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT 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 reinstituting hormone replacement therapy (HRT), 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 woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' 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 SANDRENA, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen 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 erythematosus*
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis
- Angioedema (hereditary and acquired).

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Coronary Artery Disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women, with or without existing CAD, who received combined oestrogen-progestin

or oestrogen-only HRT.

Combined oestrogen-progestin therapy

The relative risk of CAD during use of combined oestrogen+progestin HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestin use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only

Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Endometrial hyperplasia and carcinoma

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see *section 4.8 Undesirable effects*). After stopping treatment risk may remain elevated for at least 10 years.

The addition of a progestin cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestin therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

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.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestins to oestrogen replacement therapy should be considered in women, who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

Breast cancer

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen 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 oestrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see *section 4.8 Undesirable effects*).

Oestrogen-only therapy:

The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-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 oestrogen-progestogen combinations (see *section 4.8 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.

HRT, especially oestrogen-progestogen combined treatment, increase the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

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

Some other studies, including the Women's Health Initiative (WHI) trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see *section 4.8 Undesirable effects*).

Venous thromboembolism

HRT is associated with a 1.3-3 fold 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 (see *section 4.8 Undesirable effects*).

Patients with a history of VTE or 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 use of oestrogens, older age, major surgery, prolonged immobilization, obesity (BMI>30 kg/m^2), pregnancy/postpartum period, systemic *lupus erythematosus* (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

As in all postoperative patients prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. 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 thrombosis at 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 use of HRT.

If VTE develops after initiating therapy, SANDRENA 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, dyspnea).

Ischaemic stroke

Combined oestrogen-progestin and oestrogen-only therapies 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 (see *section 4.8 Undesirable effects*).

Other conditions

Oestrogen may cause fluid retention and therefore patients with cardiac or renal dysfunction should be carefully observed.

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

Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Oestrogens 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 radioimmunoassay) 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-1-antitrypsin, ceruloplasmin.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should minimise exposure to the sun or ultraviolet radiation whilst taking HRT.

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 oestrogen-only HRT after the age of 65.

SANDRENA is not a contraceptive and adequate non-hormonal contraception should be advised.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and withoutribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co- administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See *section 4.5 Interaction with other medicines and other forms of interaction*.

Potential estradiol transfer to children

Estradiol gel can be accidentally transferred to children from the area of the skin where it was applied on.

Post-marketing reports of breast budding and breast masses in prepubertal females, precocious puberty, gynaecomastia and breast masses in prepubertal males following unintentional secondary exposure to estradiol spray/gel have been reported. In most cases, the condition resolved with removal of estradiol exposure.

Patients should be instructed:

- not to allow others, especially children, to come into contact with the exposed area of the skin and to cover the application site with clothing if needed. In case of contact the child's skin should be washed with soap and water as soon as possible.
- to consult a physician in case of signs and symptoms (breast development or other sexual changes) in a child that may have been exposed accidentally to estradiol gel.

Excipients

This medicinal product contains 62.5 - 187.5 mg propylene glycol in each 0.5 - 1.5 g dose and may cause skin irritation.

This medicinal product contains 271 - 835 mg alcohol (ethanol) in each dose of 0.5 - 1.5 g. It may cause burning sensation on damaged skin.

4.5 Interaction with other medicines and other forms of interaction

The metabolism of oestrogens may be increased by concomitant use of substances, known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors, can increase or decrease plasma concentrations of oestrogen. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant medications including HIV/HCV antivirals should be consulted to identify potential interactions and any related recommendations.

Herbal preparations, containing St John's wort (*Hypericum perforatum*), may induce the metabolism of oestrogens.

At transdermal administration, the first-pass effect in the liver is avoided and thus transdermally applied oestrogens might be less affected than oral hormones by enzyme inducers.

Clinically an increased metabolism of oestrogens and progestins may lead to decreased effect and changes in the uterine bleeding profile.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol containing medications such as CHCs.

Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see *section 4.4 Special warnings and precautions for use*).

4.6 Fertility, pregnancy and lactation

Pregnancy

SANDRENA is not indicated during pregnancy. If pregnancy occurs during medication with SANDRENA treatment should be withdrawn immediately).

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to

oestrogens indicate no teratogenic or foetotoxic effects.

Breastfeeding

SANDRENA is not indicated during lactation.

Fertility

No data is available

4.7 Effects on ability to drive and use machines

Oestrogens such as SANDRENA do not affect the ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions occur most commonly during the first months of treatment. They are usually mild and subside with continued treatment.

Adverse drug reactions were recorded e.g. in 3 phase III clinical studies (n = 611 women at risk) and were included in the table when considered at least possibly related to treatment with 50 mcg/day estradiol or 100 mcg/day estradiol, respectively, following transdermal application.

The table below lists adverse drug reactions recorded in clinical studies as well as adverse drug reactions reported post-marketing. The experience of adverse drug reactions is overall expected in 76% of the patients. Adverse drug reactions appearing in > 10% of patients in clinical trials were application site reactions and breast pain.

Undesirable effects according to system organ class associated with transdermal estradiol treatment are presented in the table below:

Organ system class	**Common ADRs, ≥1/100 <1/10**	**Uncommon ADRs, ≥1/1 000 <1/100**	**Rare ADRs, ≥1/10 000 <1/1 000**	**Adverse events reported post marketing with frequency not known (cannot be estimated from the available data)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Benign breast neoplasm, benign endometrial neoplasm		Uterine fibroids
Immune system disorders		Hypersensitivity reaction		Exacerbation of angioedema (hereditary and acquired)
Metabolism and nutrition disorders	Oedema, weight increase, weight decrease	Increased appetite, hypercholesterolemia[1]		
Psychiatric disorders	Depression, nervousness, lethargy	Anxiety, insomnia, apathy, emotional lability, impaired concentration, changes in mood or libido, euphoria[1], agitation[1]		
Nervous system disorders	Headache, dizziness	Migraine, paraesthesia, tremor[1]		

Organ system class	**Common ADRs, ≥1/100 <1/10**	**Uncommon ADRs, ≥1/1 000 <1/100**	**Rare ADRs, ≥1/10 000 <1/1 000**	**Adverse events reported post marketing with frequency not known (cannot be estimated from the available data)**
Eye disorders		Visual impairment, dry eye[1]	Contact lense intolerance	
Cardiac disorders		Palpitations		
Vascular disorders	Hot flushes	Hypertension[1], superficial phlebitis[1], purpura[1]	Venous thromboembolism (i.e. deep leg or pelvic venous thrombosis and pulmonary embolism)[2]	Cerebral ischaemic events
Respiratory, thoracic and mediastinal disorders		Dyspnoea[1], rhinitis[1]		
Gastrointestinal disorders	Nausea, vomiting, stomach cramps, flatulence	Constipation, dyspepsia[1], diarrhoea[1], rectal disorder[1]		Abdominal pain, bloating (abdominal distension)
Hepatobiliary disorders			Alterations in liver function and biliary flow	Cholestatic jaundice
Skin and subcutaneous tissue disorders		Acne, alopecia, dry skin, nail disorder[1], skin nodule[1], hirsutism[1], erythema nodosum, urticaria	Rash	Contact dermatitis, eczema
Musculoskeletal and connective tissue disorders		Joint disorders, muscle cramps		
Renal and urinary disorders		Increased urinary frequency/urgency, urinary incontinence[1], cystitis[1], urine discoloration[1], haematuria[1]		
Reproductive system and breast disorders	Breast pain/tension, unscheduled vaginal bleeding or spotting, vaginal discharge, disorder of vulva/vagina, menstrual disorder	Breast enlargement, breast tenderness, endometrial hyperplasia, uterine disorder[1]	Dysmenorrhea, pre-menstrual like syndrome	

Organ system class	Common ADRs, ≥1/100 <1/10	Uncommon ADRs, ≥1/1 000 <1/100	Rare ADRs, ≥1/10 000 <1/1 000	Adverse events reported post marketing with frequency not known (cannot be estimated from the available data)
General disorders and administration site conditions	Skin irritation, application site pruritus, pain, increased sweating	Fatigue, abnormal laboratory test[1], asthenia[1], fever[1], flu syndrome[1], malaise[1]		

1. have been reported in single cases in clinical trials. Given the small study population (n = 611) it cannot be determined based on these results if the events are uncommon or rare.

2. see section 4.3 *Contraindications* and *section 4.4 Special warnings and precautions for use*.

Other adverse reactions have been reported in association with oestrogen- progestin treatment:

- Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer
- Myocardial infarction and stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme
- Probable dementia over the age of 65 (see *section 4.4 Special warnings and precautions for use*).

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestogen 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.

Largest meta-analysis of prospective epidemiological studies

Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m²)

Age at start 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
		Oestrogen only HRT	
50	13.3	1.2	2.7
		Combined oestrogen-progestogen	
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.

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

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1000 HRT users after 10 years
		Oestrogen only HRT	
50	26.6	1.3	7.1
		Combined oestrogen-progestogen	
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.

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestogen ‡	
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.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see *section 4.4 Special warnings and precautions for use*).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestin to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestin 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 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-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:

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
Oral, oestrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral, combined oestrogen-progestogen			
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 oestrogen-progestin HRT over the age of 60 (see *section 4.4 Special warnings and precautions for use*).

Risk of ischaemic stroke

The use of oestrogen-only and oestrogen + progestin therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

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, *section 4.4 Special warnings and precautions for use*.

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
50-59	8	1.3 (1.1 1.6)	3 (1-5)

*no differentiation was made between ischaemic and haemorrhagic stroke.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Generally, oestrogens are well tolerated even in massive doses. Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. Nausea, vomiting and withdrawal bleeding may occur in some women.

Overdose effects generally lead to breast tenderness, abdominal or pelvis swelling, anxiety and irritability. These symptoms disappear when the treatment is stopped or when the dose is reduced.

Overdosage is unlikely with transdermal application. There is no specific antidote and treatment should be symptomatic. The gel should be washed.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural and semisynthetic estrogens, plain, ATC code: G03CA03.

The active ingredient in SANDRENA, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Oestrogens prevent bone loss following menopause or ovariectomy.

Clinical trial information

The pharmacodynamics of SANDRENA are similar to those of oral oestrogens but the major difference to oral administration lies in the pharmacokinetic profile.

The clinical efficacy of SANDRENA in the treatment of menopausal symptoms is comparable to that of peroral oestrogen.

Relief of oestrogen-deficiency symptoms and bleeding patterns

Relief of menopausal symptoms was achieved during the first few weeks of treatment.

Prevention of osteoporosis

Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass.

The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestin – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

5.2 Pharmacokinetic properties

SANDRENA is an alcohol-based estradiol gel. When applied to the skin the alcohol evaporates rapidly and estradiol is absorbed through the skin into circulation. Application of SANDRENA on area of 200–400 cm^2 (size of one to two hands) does not affect the amount of estradiol absorbed. However, if SANDRENA is applied to larger area absorption decreases significantly. To some extent, however, the estradiol is stored in subcutaneous tissue from where it is released gradually into circulation. Percutaneous administration circumvents the hepatic first-pass metabolism. For these reasons the fluctuations in the plasma oestrogen concentrations with SANDRENA are less pronounced than with peroral oestrogen.

Percutaneous doses of 0.5, 1.0 and 1.5 mg of estradiol (0.5, 1.0 and 1.5 g SANDRENA) result in mean C_{max} concentrations in plasma of 143, 247 and 582 pmol/l, respectively. The corresponding mean $C_{average}$ concentrations over the dosing interval are 75, 124 and 210 pmol/l. The corresponding mean C_{min} concentrations were 92, 101 and 152 pmol/l, respectively.

During SANDRENA treatment the estradiol/oestrone ratio remains between 0.4 and 0.7, while for oral oestrogen treatment it usually drops to less than 0.2. The mean estradiol exposure at steady state of SANDRENA is 82 percent compared with an equivalent oral dose of estradiol valerate.

Otherwise, the metabolism and excretion of transdermal estradiol follow the fate of natural oestrogens.

5.3 Preclinical safety data

Estradiol is a natural female hormone with an established clinical use, therefore no toxicological

studies have been performed with SANDRENA. The necessary studies on the irritant effects of the gel were studied in rabbits and skin sensitisation in guinea pigs. Based on the results from these studies it can be concluded that SANDRENA very infrequently could cause mild skin irritation. Skin irritation can be reduced by daily change of the application site.

Environmental Risk Assessment (ERA)

The environmental risk assessment has shown that this medicinal product may pose a risk to the aquatic environment (see *section 6.6 Special precautions for disposal*).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 974P
Trolamine
Propylene glycol
Purified water
Ethanol 96%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

SANDRENA is available in single-dose sachets (aluminium laminated with PVC/paper).

Pack sizes:

0.5 g sachets: 28 or 91 sachets.
1 g sachets: 28 or 91 sachets.

Not all pack sizes may be available.

6.6 Special precautions for disposal

This medicine may pose a risk to the environment (see *section 5.3 Preclinical safety data*).

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Orion Pharma (NZ) Limited
c/o Max Health Ltd
PO Box 44452
Auckland 1246

Telephone: (09) 815 2664

9 DATE OF FIRST APPROVAL

1 May 2025

10 DATE OF REVISION OF THE TEXT

16 February 2026

Summary table of changes

Section Changed	Summary of new information
1, 2	Editorial correction to the expression of the active ingredient (as hemihydrate)
2, 3, 6.5	Minor editorial updates for clarity
4.2	Wording changes without a change to actual dose. Information added on when to begin treatment for women using HRT. Added that lowest effective dose for the shortest duration should be used.
4.3	Contraindications updated.
4.4	Special warnings and precautions for use have been updated. Added a section with a list of conditions which need supervision. Updated information regarding ALT elevations.
4.5	Added information on transdermal applied oestrogens possibly being less affected than oral hormones by enzyme inducers due to first-pass effect in the liver being avoided. Added information on the effect of HRT with oestrogens on other medicinal products. Updated pharmacodynamic interactions information.
4.6	Added for pregnancy that '*the results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects*.'
4.8	Table added listing the frequency of undesirable effects recorded in clinical studies and reported post-marketing according to system organ class associated with transdermal estradiol treatment. Added list of other adverse reactions that have been reported in association with estrogen/progestin treatment.
4.9	More information has been added for overdose.
5.1, 5.2	Pharmacodynamic and pharmacokinetic section has been updated.
5.3	Carcinogenicity section has been removed. Information is included in other section of the data sheet. Added information on the environmental risk assessment.
6.1	Corrected Carbomer number to 974P.
6.6	Added that this medicine may pose a risk to the environment.