New Zealand Data Sheet

1 PRODUCT NAME

SANDRENA, estradiol 0.1%, gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SANDRENA gel contains estradiol 1 mg/g.

Each sachet contains either 0.5 mg or 1.0 mg of estradiol.

Excipient with known effect:

One gram of gel contains 585 mg ethanol (see *section 4.4 Special warnings and precautions for use*).

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

3 PHARMACEUTICAL FORM

Gel.

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 (estrogen 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 is used either cyclically or continuously, in individually adjusted doses of 0.5 g to 1.5 g per day, corresponding to 0.5 to 1.5 mg estradiol per day. Most patients usually start with a 1.0 mg estradiol dose daily. This can be adjusted after 2 to 3 cycles.

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

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

Method of administration

Apply on dry and clean skin.

One to two dose units (0.5 g or 1.0 g) of SANDRENA (0.5 to 1.5 mg estradiol) are applied once daily on the skin of the lower trunk or the thigh. The application surface area should be one to two times the size of the hand. SANDRENA should not be applied on the breasts, on the face or on irritated or broken 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 thoroughly 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 cleansed before situations where skin-to-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 contact to others (e.g. child, spouse, pets). This may cause adverse effects if the gel is transferred. 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 (see section 4.4 Special warnings and precautions for use).

In clinical trials the use of SANDRENA has induced dermal irritation only very infrequently. The probability of topical irritation can be further decreased by changing the area of application daily (e.g. left and right side on alternate days).

If the patient forgets to apply a dose, it should be applied as soon as possible, unless the dose is more than 12 hours late. If the dose is more than 12 hours late, it should be skipped. Missed doses may induce breakthrough bleeding.

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.

Monitoring advice

As for all steroids with hormonal activity, yearly medical examination particularly of the breasts and pelvic areas is advisable. Review the need for continuation of treatment after 6 months (see *section 4.4 Special warnings and precautions for use* and *section 4.1 Therapeutic indications*).

4.3 Contraindications

- Undiagnosed vaginal or genital bleeding.
- Cerebrovascular disorders
- Active or recent arterial thromboembolic diseases (e.g. angina, myocardial infarction) or thrombophlebitis
- Acute liver disease, history of liver disease where liver function has failed to return to normal or severe hepatic disease (including Dubin Johnson and Rotors' syndrome)
- Known, past or suspected malignancy of the genitals or breasts
- Pregnancy
- Non hysterectomised women without concomitant progestogen
- Known or suspected estrogen-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)
- 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

Identified precautions

The benefits and risks of hormone treatment (HT), including SANDRENA must always be carefully weighed, including consideration of the emergence of risks as therapy continues. SANDRENA should be used for the shortest duration consistent with treatment goals. The need for continued treatment should be reviewed after 6 months. SANDRENA should only be continued for as long as the benefit outweighs the risks.

Do not use in combination with a progestogen in hysterectomised women.

Check the following before use

Before therapy is initiated or reinstituted, a complete gynaecological examination should be performed and repeated at least once a year in long-term replacement therapy. A careful appraisal of the risks and benefits should be undertaken before use and after 6 months, and SANDRENA should only be continued as long as the benefit outweighs the risk.

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)

Hormone treatment should not be initiated or continued to prevent or treat cardiovascular disease. There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated estrogens and MPA. Large clinical trials showed a possible increased risk of cardiovascular morbidity in the first year of use and no benefit thereafter. For other HT products there are only limited data from randomised controlled trials examining benefit in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HT products.

The relative risk of CAD during use of combined estrogen+progestin hormone replacement therapy (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 estrogen+progestin use is very low in healthy women close to menopause, but will rise with more advanced age.

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

Endometrial hyperplasia and carcinoma

The risks and benefits of treatment should be evaluated and close monitoring performed for patients with: Endometriosis. Endometrial hyperplasia (simple glandular hyperplasia or hyperplasia glandularis cystica). Pre-existing uterine leiomyoma can increase in size under estradiol treatment. In these patients, careful examinations should be performed at regular intervals during therapy.

In women with an intact uterus 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 greater compared with non-users, depending on the duration of treatment and estrogen dose. 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 estrogen-progestin therapy in non-hysterectomised women prevents the excess

risk associated with estrogen-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 estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestins to estrogen 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 estrogen-progestogen or estrogen-only HRT, that is dependent on the duration of taking HRT.

Combined estrogen-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 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-progestogen 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 on this therapy, in particular those with fibrocystic disease of the breast or a family history of breast cancer (first degree relatives), should have regular breast examinations and should be instructed in breast self-examination. It is recommended that mammography be performed before the start of treatment and repeated at regular intervals. Mammographic density may be increased after the use of combined HT. This may have implications for the sensitivity and specificity of breast cancer screening.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests an increased risk in women taking estrogen-only or combined estrogen-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 risk.

Venous thromboembolism

Oral HT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The studies found a two- to threefold higher risk for users compared with non-users, which for healthy women amounts to 1 to 2 additional cases of VTE in 10,000 patient years of treatment with HT. This increased risk may not apply for transdermal estrogens (see *section 5.1 Pharmacodynamic properties – Clinical trials*).

The occurrence of such an event is more likely in the first year of HT than later. Generally recognized risk factors for VTE include a personal history or family history, severe obesity

(BMI>30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE. Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HT may add to this risk. 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 HT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HT. The risk of VTE may be temporarily increased with prolonged immobilization, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilization is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilized.

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, dyspnea).

The concurrent use of SANDRENA and other estrogenic or partial estrogenic agents has not been studied and is, therefore, not recommended as its use may contribute to long-term risk.

Ischaemic stroke

Combined estrogen-progestin and estrogen-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.

Other conditions

Some conditions may be aggravated during estrogen therapy. Women on estradiol treatment with one of the following conditions (or with a history thereof during previous pregnancy or hormone use) should therefore be closely monitored. These conditions include: hypertension, hypertriglyceridemia, migraine or severe headache, benign breast disease, liver function disturbances, cholestasis, cholelithiasis, diabetes mellitus with or without vascular involvement, asthma, otosclerosis, multiple sclerosis, galactorrhea, elevated prolactin levels, history of herpes gestationis, epilepsy and angioedema (hereditary or acquired), severe disturbance of the lipid metabolism, renal dysfunction, systemic lupus erythematosus, metabolic bone disease associated with hypercalcaemia.

Since estrogen may cause water retention, patients with heart failure, renal dysfunction or severe hypertension should be observed closely.

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.

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

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 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 does not improve cognitive function. There is some evidence of increased risk of probable dementiain women who start using continuous combined or estrogen-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 with and without dasabuvir, 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, 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, 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 combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See *section 4.5 Interactions with other medicines and other forms of interactions*.

Potential estradiol transfer to children

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

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 product contains propylene glycol and may cause skin irritation.

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

Use in the elderly

No data is available

Paediatric use

No data is available

Effects on laboratory tests

No data is available

4.5 Interactions with other medicines and other forms of interactions

The metabolism of estrogens 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 HCF inhibitors, can increase or decrease plasma concentrations of estrogen. 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 estrogens.

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

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, 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. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, 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 combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see *section 4.4 Special warnings and precautions for use*).

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data is available

Use in pregnancy – Pregnancy Category B3[1]

Estrogens must not be used during pregnancy. If pregnancy occurs, treatment should be withdrawn immediately (see *section 4.3 Contraindications* and *section 4.4 Special warnings and precautions for use*).

Use in lactation

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of milk. Detectable amounts of estrogens and progestogens have been found in the milk of lactating mothers receiving these compounds, but the effects on the breastfed infant have not been determined. Estrogens must not be used during lactation.

[1] Australia Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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/

Adverse events reported at an incidence of >1% among patients treated with SANDRENA during controlled trials are shown in the table below:

Table 1: Adverse events reported at an incidence of >1% among patients treated with SANDRENA during controlled trials.

System organ class	PRODUCT (N=623) %	CONTROLS (N=256) %
Infections and infestations (Total %)	(1.61)	-
Infectious disease	1.61	-
Metabolism and nutrition disorders (Total %)	(12.04)	(13.67)
Oedema	8.99	13.28
Weight increase	2.41	-
Psychiatric disorders (Total %)	(1.61)	(4.30)
Sleep disorders	0.32	1.17
Nervousness	0.64	1.17
Depression	0.48	1.95
Central and peripheral nervous system (Total %)	(6.58)	(8.98)
Headache	4.49	6.25
Dizziness	1.28	0.78
Cardiac disorders (Total %)	(1.28)	(1.56)
Cardiac symptoms (e.g. palpitations)	1.28	1.56
Vascular disorders (extracardiac) (Total %)	(5.46)	(3.52)
Menopause symptoms	2.89	2.34
Varicose veins	2.09	0.78
Respiratory thoracic and mediastinal disorders (Total %)	(1.77)	(3.13)
Infection upper respiratory tract	1.28	2.34
Gastrointestinal disorders (Total %)	(4.33)	(7.03)
Nausea	1.44	1.56
Gastrointestinal symptoms	2.41	5.47
Skin and appendages (Total %)	(4.01)	(21.48)
Skin irritation	3.90	21.09
Musculo-skeletal (Total %)	(2.56)	(3.91)
Skeletal/back pain	1.93	1.95
Urinary system disorders (Total %)	(0.64)	(1.17)
Urinary problems	0.64	1.17

Reproductive disorders (Total %)	(22.31)	(17.97)
Mastalgia	17.50	11.72
Breakthrough bleeding, spotting	2.41	2.34
Leucorrhoea	1.77	3.13
Dysmenorrhoea	1.52*	3.13**
Body as a whole-general disorders (Total %)	(4.01)	(1.17)
Fatigue	2.25	1.17

*As counted from study 63808 from AE listing where 6 patients were scored as having dysmenorrhoea out of 395 patients.
**As counted from all studies where eight patients out of 256 reported abdominal pain or abdominal cramps.

In clinical trials dermal irritation has occurred in less than 4% of the patients.

Side effects are most common in the first months of the treatment. They are usually mild, only seldom leading to discontinuation of the treatment.

Estimates from post marketing surveillance

The experience of adverse drug reactions is overall expected in 76% of the patients. Undesirable effects according to system organ class associated with transdermal estradiol treatment are presented below:

Adverse events reported post marketing with frequency not known (cannot be estimated from available data): Uterine fibroids, exacerbation of hereditary angioedema, cerebral ischaemic events, abdominal pain, bloating (abdominal distension), cholestatic jaundice, contact dermatitis and eczema.

Common (≥1% - < 10%): skin irritation, myalgia, headache, dizziness, gastrointestinal symptoms (nausea, vomiting, stomach cramps, flatulence), oedema, weight increase, cardiac symptoms, varicose veins, mastalgia, vaginal spotting, vaginal discharge, disorder of vulvar/vagina, menstrual disorder, dysmenorrhoea, fatigue, depression, nervousness, lethargy, hot flushes, application site pruritis, pain and increased sweating.

Uncommon (≥0.1% - < 1%): itching, erythema, chloasma, myalgia, arthralgia, arthropathy, neurological disorders, anxiety, apathy, emotional lability, impaired concentration, changes in mood or libido, migraine, paraesthesia, palpitations, vision disturbances, tinnitus, sleep disorders (incl. insomnia), amnesia, hypertension, thrombosis & thrombophlebitis, urinary problems (incl. increased urinary frequency/urgency), constipation, pruritus genital, uterine fibroid, endocervical polyp, Ca adenopapillaris corporis uteri, pelvic pain, leg pain, benign breast neoplasm, benign endometrial neoplasm, increased appetite, acne, alopecia, dry skin, joint disorders, muscle cramps, breast enlargement, breast tenderness and endometrial hyperplasia.

Rare (>0.01% - <0,1%): venous thromboembolism, alterations in liver function and biliary flow and rash.

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

Breast cancer risk

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

Table 2: 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
		Estrogen only HRT	
50	13.3	1.2	2.7
		Combined estrogen-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.

Table 3: 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
		Estrogen only HRT	
50	26.6	1.3	7.1
		Combined estrogen-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.

Table 4: 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 estrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA estrogen & 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 an uterus not using HRT.

In women with a uterus, use of estrogen-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 estrogen-only use and estrogen 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 progestogen to estrogen-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 estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed.

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 50-54 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 HT (see *section 4.4 Special warnings and precautions for use*). Results of the WHI studies are presented:

Table 5: 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 estrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined estrogen-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 estrogen-progestogen 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 + progestogen 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*.

Table 6: 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.

4.9 Overdose

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

Generally, estrogens are well tolerated even in massive doses. Possible symptoms include those listed under adverse drug reaction. Management is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

SANDRENA is an alcohol-based, percutaneously applied gel for hormone replacement therapy with estradiol as its active ingredient. The pharmacodynamics of SANDRENA are similar to those of oral estrogens 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 estrogen. Combined with medroxyprogesterone acetate, percutaneous estradiol treatment lowers total cholesterol without reducing the HDL cholesterol level.

Clinical trials

Different adverse reaction rates have been reported with the use of different transdermal estrogen replacement therapy regimens. Depending on the formulation of the transdermal regimens, gel or patch, the rate of skin irritation varies and is considerably lower with the gel formulation.

In clinical trials with 0.5 - 1.5 g SANDRENA (0.5 - 1.5 mg estradiol) 659 women have been treated for 1 – 2 years. SANDRENA has been equally effective alleviating climacteric symptoms as oral estradiol valerate tablets or a transdermal patch. SANDRENA treatment has also rendered an acceptable bleeding pattern compared with oral or other transdermal regimens.

In a clinical trial with 395 women only 3% discontinued the study due to adverse events. The adverse reaction profile and rate with SANDRENA has been similar to that of oral and other transdermal regimens. In clinical trials with SANDRENA less than 5% of the patients have reported skin irritation while the percentage with the comparative transdermal patch reached over 30%. The aforementioned studies were, conducted prior to the WHI and Million Women studies. [See *section 4.1 Therapeutic indications* and *section 4.2 Dose and method of administration* for recommended clinical use.]

In a large randomised trial involving women who received hormone replacement therapy for an average of 5.2 years using conjugated equine estrogens (0.625 mg/day) continuously combined with medroxyprogesterone acetate (2.5 mg/day), adverse effects on cardiovascular disease and the incidence of breast cancer were observed. The Women's Health Initiative study was designed to investigate the efficacy and safety of long-term hormone replacement therapy (HT) in preventing coronary heart disease in healthy postmenopausal women with an intact uterus.

The relative risk of coronary heart disease was 1.29 (95% confidence interval 1.02-1.63),corresponding to an increase in the absolute rate from 30 to 37 per 10 000 person-years. The increased risk of breast cancer became apparent after 4 years on study medication. The relative risk of stroke was 1.41 (1.07-1.85), an increase in the absolute rate from 21 to 29 per 10 000 person-years. The relative risk of VTE was 2.11 (1.58-2.82), an increase from 16 to 34 per 10,000 person-years. The relative risk of breast cancer was 1.26 (1.00-1.59), an increase from 30 to 38 per 10 000 person-years. The study was stopped prematurely because the pre-set criterion for invasive breast cancer was fulfilled and a global risk-benefit index supported risks exceeding benefits. In the estrogen only arm global risk-benefit index has not been exceeded, and that arm is continuing. The risks and benefits in women receiving treatment for

the short- term management of climacteric symptoms of estrogen deficiency or for the management of premature menopause were not examined. In a randomised controlled subgroup of the WHI trial (referred to as the WHI Memory Study, WHIMS), women of 65 years of age or older (n=4,532, 50% older than 70) treated with conjugated equine estrogens (0.625 mg/day) continuously combined with medroxyprogesterone acetate (2.5 mg/day) 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 in the estrogen plus progestogen group compared to 22 per 10,000 in the placebo group.

It is unknown if these findings apply to younger postmenopausal women.

An observational study of 1,084,110 women, (the Million Women Study) of whom 828,923 were postmenopausal has shown that, compared to never-users, use of estrogen-progestogen combined HT is associated with a higher risk of breast cancer (RR=2.00, 95%CI:1.88-2.12) than use of estrogens alone (RR=1.30, 95%CI:1.21-1.40). In this study the magnitude of the increase in breast cancer risk was similar for all estrogen-only preparations, irrespective of the type, dose or route of administration of the estrogen (oral RR=1.32, 95%CI:1.21-1.45; transdermal RR=1.24, 95%CI:1.11-1.39 and implanted RR=1.65, 95%CI:1.26-2.16). Likewise, the magnitude of the increased risk was similar for all estrogen plus progestogen preparations, irrespective of the type of progestogen or the number of days of addition per cycle (sequential<5 years RR=1.77, 95%CI:1.59 -1.97 and ≥5 years RR=2.12, 95%CI:1.95-2.30; continuous <5 years RR=1.57, 95%CI:1.37-1.79 and ≥5 years RR=2.40, 95%CI:2.15-2.67). For all HT, an excess risk becomes apparent within 1-2 years of starting treatment and increases with duration of use of HT but begins to decline when HT is stopped and by 5 years reaches the same level as in women who have never taken HT. The increase in risks applies to all women studied, although the relative risk in all current users of HT was significantly higher in those with a lean or normal body build (body mass index or BMI of <25kg/m^2; RR=1.97, 95%CI:1.82-2.14) compared to those with a BMI of ≥ 25 kg/m^2; RR=1.46, 95%CI:1.36-1.58) [see *section 4.4 Special warnings and precautions for use*].

5.2 Pharmacokinetic properties

SANDRENA is an alcohol-based estradiol gel. When applied to the skin the gel evaporates rapidly and estradiol is absorbed through the skin into circulation. To some extent, however the estradiol is stored in subcutaneous tissue from where it is released gradually into circulation.

Percutaneous administration naturally circumvents the hepatic first-pass metabolism.

Because of the change in composition, the new formulation was compared to the old formulation of SANDRENA in a bioequivalence study. Twenty-seven study subjects were postmenopausal Caucasian females, 50 - 70 years of age, non-smoker, their BMI was 19-30 kg/m^2 and they had normal gynaecological status. The study was a multiple-dose, single-blind, randomised, crossover trial without washout period. Both treatments consisted of application of 1 gram of the gel on a skin area of 400 cm^2 (thigh) once daily for 14 consecutive days. The new formulation was bioequivalent with the old formulation. The estimate for the ratio (the new/the old formulation) of extent of drug absorption, $AUC_{(0\text{-}24h)}$, was 1.05. The associated 90 % confidence interval (89.7 - 123 %) was included within the bioequivalence range of 80 - 125 %. The estimate for the ratio (the new / the old formulation) of the rate of absorption, C_{max}, was 1.06. The associated 90 % confidence interval (87.9 - 128 %) was included. The wider confidence interval for C_{max} was justified because transdermal estradiol can be considered as a highly variable drug.

Table 7: 90% Confidence-intervals of ratio C/A (SANDRENA new / old formulation)

Parameter (mean±SD)	Formulation C (=new) batch BE036L2A	SANDRENA A (=old) batch BEC16B	90% C.I., ratio estimate (log transformed data)
$AUC_{(0\text{-}24)}$ (pmol*h/l)	2696 ± 2337	2108 ± 890	89.7 – 123 %, 1.05

C_{max} (pmol)	157 ± 129	148 ± 118	87.9 – 128 %, 1.06

During SANDRENA treatment the estradiol/estrone ratio remains at 0.7, while during peroral estrogen treatment it usually drops to less than 0.2. The steady state bioavailability of SANDRENA is 82 per cent compared to the equivalent oral dose of estradiol valerate.

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

5.3 Preclinical safety data

Genotoxicity

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 have been 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. The frequency of the occurrence of dermal irritation can be reduced by daily change of the application site.

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 micronuclei formation in rodent bone marrow micronucleus assays.

Carcinogenicity

Supraphysiological 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. Unopposed estrogen therapy is associated with an increased incidence of endometrial carcinoma, particularly with prolonged use.

Concurrent progestogen therapy for a minimum of 12 to 14 days reduces the risk of endometrial hyperplasia, (see *section 4.2 Dose and method of administration*). Usually, a withdrawal bleed resembling normal menstruation will occur after the progestin period. Unexpected or prolonged uterine bleeding during therapy should be reported to the physician and its cause clarified.

Breast cancer

Epidemiological studies indicated a small or moderate increase in the probability of having breast cancer in women currently or recently using hormone treatment (HT). A large observational study, the Million Women Study, has shown that compared to never-users, use of estrogen-progestogen combined HT is associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88-2.12) than use of estrogens alone (RR = 1.30, 95%CI 1.21-1.40). A large randomised clinical trial demonstrated that continuous combined HT is associated with an increase in breast cancer risk (RR 1.26, 95% CI: 1.00-1.59) (see Women's Health Initiative in *section 5.1 Pharmacodynamic properties – Clinical trials*). In a separate arm of this trial no increased risk has so far been observed for estrogen-only therapy. The use of estrogens alone as well as combined/sequential estrogen and progestogen use is associated with an increased risk of breast cancer. This emerges towards the end of the first year of treatment (see Million Women Study in Clinical Trials).

Breast cancer can be fatal. Therefore, for all HT, the benefits and risks of treatment should be carefully considered (see *section 4.1 Therapeutic indications*). It is recommended that women are encouraged to report any changes in their breast to their doctor. Regular breast examinations and, where appropriate, mammography should be carried out, particularly in women with risk factors for breast cancer.

If prescribing HT, the potential for increased cardiovascular, thrombotic and neoplastic

adverse events, and an increased incidence of probable dementia in older women, must be considered as part of the risk-benefit assessment (see *section 5.1 Pharmacodynamic properties – Clinical trials*). The need for continuation of treatment should be reviewed after 6 months.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 934P
Trolamine,
propylene glycol
Purified water
Ethanol.

6.2 Incompatibilities

No incompatibilities have been found.

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: 28's, 91's
1 g: 7's (sample pack), 28's, 91's.

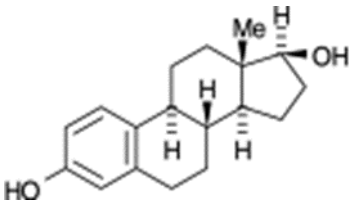
Not all pack sizes may be available.

6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure



Chemical name: 17β-estradiol; Estra-1, 3, 5 (10) - triene-3, 17β - diol

Molecular formula: $C_{18}H_{24}O_2$. Molecular weight: 272.4.

CAS number

50-28-2 (anhydrous)

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

1 May 2025

Summary table of changes

Section Changed	Summary of new information