# NEW ZEALAND DATA SHEET

## 1 PRODUCT NAME

ESTRADIOL (estradiol) 37.5, 50, 75 & 100 mcg/24* hrs Transdermal System

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1.1.1.1 Active moiety

Estradiol

2.1.1.1.2 Active substance(s)

Estradiol transdermal system is available in four sizes:

- 3.75 $cm^2$ patch containing 0.59 mg estradiol (as hemihydrate) with a nominal in vivo release rate of 37.5 micrograms (0.0375 milligrams) estradiol per day.
- 5 $cm^2$ patch containing 0.78 mg estradiol (as hemihydrate) with a nominal in vivo release rate of 50 micrograms (0.05 milligrams) estradiol per day.
- 7.5 $cm^2$ patch containing 1.17 mg estradiol hemihydrate with a nominal in vivo release rate of 75 (0.075 milligrams) micrograms estradiol per day.
- 10 $cm^2$ patch containing 1.56 mg estradiol (as hemihydrate) with a nominal in vivo release rate 100 (0.1 milligrams) micrograms estradiol per day.

*Not all strengths may be available in New Zealand*

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Transdermal patch.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

The Estradiol transdermal system regimen is indicated for the following:

- Estrogen replacement therapy for the treatment of the symptoms of natural or surgically induced menopause.

- Prevention of postmenopausal osteoporosis (see Dosage and Administration and Warnings and Precautions).

In women with an intact uterus, estrogens should always be supplemented by administration of a progestogen.

## 4.2 Dosage And Method Of Administration

#### 4.2.1.1.1 Adults and geriatric patients

Hormone replacement therapy (HRT) involving either estrogen-only or estrogen-progestogen combined therapy should only be continued as long as the benefits outweigh the risks for the individual.

Estradiol transdermal system should be applied every 3 to 4 days (i.e. twice weekly).

#### 4.2.1.1.2 Climacteric symptoms

Treatment should be initiated with the lowest dose. The lowest dose is 25 mcg/24 hrs. Depending on the clinical response the dose should be adjusted to the woman's individual needs. If, after three months, there is an insufficient response in the form of alleviated symptoms, the dose should be increased. If symptoms of overdose arise (e.g. tender breasts) the dose must be decreased. Maintenance therapy must always be at the lowest effective dose.

#### 4.2.1.1.3 Prevention of postmenopausal osteoporosis

Treatment should be initiated with the lowest dose. The lowest dose is 25 mcg/24 hrs. Dose adjustments can be made by using other strengths of Estradiol transdermal system. The lowest effective dose should be used for maintenance therapy.

#### 4.2.1.1.4 General instructions

Estradiol transdermal system is administered as **continuous** therapy (uninterrupted application twice weekly). In women with an intact uterus, Estradiol transdermal system should be combined with a progestogen approved for addition to estrogen treatment as follows:

The progestogen is added either for the last 12 to 14 days of every 4-week cycle (**continuous-sequential**) or every day without interruption (**continuous-combined**).

In women not currently taking oral estrogens or in women switching from another estradiol transdermal therapy, treatment with Estradiol transdermal system may be initiated at any convenient time. In women who are currently taking oral estrogens, treatment with Estradiol transdermal system should be initiated one week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear within one week.

#### 4.2.1.1.5 Special populations

### 4.2.2 Patients with renal and / or hepatic impairment

No studies were performed in patients with renal and hepatic impairment.

All estrogen preparations are contraindicated in patients with severe hepatic impairment (see Contraindications).

### 4.2.3 Paediatric patients

Estradiol transdermal system is not indicated for use in children.

#### 4.2.3.1.1 Method of application

The adhesive side of Estradiol transdermal system should be placed on a clean, dry area of the abdomen. ***Estradiol transdermal system should not be applied to the breasts.***

Estradiol transdermal system should be replaced twice weekly. The site of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may dislodge the patch. The patch should be applied immediately after opening the sachet and removing the protective liner. The patch should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges.

In the event that a patch should fall off, the same patch may be reapplied. If necessary, a new patch may be applied. In either case, the original treatment schedule should be continued.

If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The subsequent patch should be applied according to the original treatment schedule. The interruption of treatment might increase the likelihood of recurrence of symptoms.

## 4.3 Contraindications

Estradiol transdermal system should not be used by women with any of the following conditions:

- Known, past or suspected breast cancer,
- Known or suspected cancer of the endometrium or other estrogen-dependent neoplasia,
- Undiagnosed abnormal vaginal bleeding,
- Severe hepatic impairment,
- History of or current venous thromboembolism (VTE) (i.e.. deep vein thrombosis, pulmonary embolism),
- Known thrombophilic disorders or thrombophlebitis,
- History of or current arterial thromboembolic disease (e.g. coronary heart disease, stroke),
- Porphyria,
- Known hypersensitivity to estrogens or to any of the excipients,
- Known or suspected pregnancy,
- Breastfeeding.

## 4.4 Special Warnings And Precautions For Use

#### 4.4.1.1.1 Warnings

For all therapeutic indications, the lowest effective dose should be used and consideration should be given to the shortest duration of use. Treatment should only be continued as long as the benefits outweigh the risks for the Individual.

The Medicines Adverse Reactions Committee advises that combined HRT should not be used for longer than 3 – 4 years.

#### 4.4.1.1.2 Osteoporosis

When initiating HRT for the prevention of osteoporosis, careful consideration should be given to the benefits versus the risks for the individual. Potential alternative therapies should be

considered if the risks outweigh the benefits. Periodic re-evaluation for continuing treatment is recommended.

#### 4.4.1.1.3 Contact sensitisation

Contact sensitisation is known to occur with all topical applications. Although it is extremely rare, women who develop contact sensitisation to any of the components of the patch should be warned that a severe hypersensitivity reaction may occur with continuing exposure to the causative agent.

#### 4.4.1.1.4 Cardiovascular disease

HRT should not be used for the prevention of cardiovascular disease.

Large clinical trials (Women's Health Initiative and Heart and Estrogen/Progestin Replacement study) evaluated the risk of cardiovascular events with the HRT products used in these studies.

The Women's Health Initiative (WHI) studies were randomised clinical trials conducted with either continuous combined oral conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) for an average follow-up of 5.2 years, or with oral CEE for an average follow-up of 6.8 years. In the WHI continuous combined oral HRT trial, the absolute excess risk of coronary heart disease was 7 additional cases per 10,000 person-years (37 versus 30) in HRT-treated women and the relative risk was 1.29. In the WHI estrogen-only HRT trial, the use of CEE alone did not affect coronary heart disease incidence in postmenopausal women [11].

In addition, both WHI studies showed an increased incidence of stroke. In the trial of continuous combined oral CEE and medroxyprogesterone acetate (MPA), the absolute excess risk was 8 additional cases per 10,000 person-years (29 versus 21) in HRT-treated women and the relative risk was 1.41. The absolute excess risk in the trial of continuous oral CEE was 12 additional cases per 10,000 person-years (44 versus 32) in HRT-treated women and the relative risk was 1.39.

The Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial using CEE and MPA for secondary prevention in postmenopausal women with documented heart disease, showed an increased risk of cardiovascular events in the first year of use and no cardiovascular benefit thereafter.

There have been no randomised controlled trials to date to assess the risk of cardiovascular morbidity or mortality, or stroke, with combined transdermal estrogen- progestogen HRT products. Therefore there are no data to support the conclusion that the frequency of cardiovascular events and stroke is different with Estradiol transdermal system.

#### 4.4.1.1.5 Venous thromboembolism

Estrogen-only and combined estrogen-progestogen HRT are associated with a higher risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism.

Some randomised controlled trials (e.g. WHI estrogen-alone, WHI combined HRT and HERS), and epidemiological studies have found a two- to three-fold higher risk for users compared with non-users.

The WHI continuous combined study (see subsection Cardiovascular disease) showed an increased incidence of pulmonary embolism. The absolute excess risk was 8 additional cases per 10,000 person-years (15 versus 7) in HRT-treated women and the relative risk was 2.13.

The increase in risk was found only in current users and did not persist in former users. The risk appeared to be higher in the first years of use compared to later years.

For non-users, it is estimated that the number of cases of VTE that would occur over a 5-year period is about 3 per 1000 women aged 50 to 59 years and 8 per 1000 women aged 60 to 69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE would be between 2 and 6 per 1000 women aged 50 to 59 years and between 5 and 15 per 1000 women aged 60 to 69 years.

Risk/benefit should therefore be carefully weighed in consultation with the individual when prescribing HRT to women with a risk factor for the occurrence of VTE that is not already mentioned under Contraindications.

Generally recognised risk factors for VTE include a personal history or family history of thromboembolic disease (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition) obesity (Body Mass Index > 30 $kg/m^2$) and systemic lupus erythematosus (SLE). The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

A history of recurrent spontaneous abortions should be investigated to exclude thrombophilic predisposition. In women in whom this diagnosis is confirmed, the use of HRT is viewed as contraindicated.

The risk of VTE may be temporarily increased by prolonged immobilisation, major elective or posttraumatic surgery, or major trauma. In women on HRT, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Depending on the nature of the event and the duration of immobilisation, consideration should be given to temporarily stopping HRT several weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobile.

Women should be told to contact their doctor immediately if they become aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

If venous thromboembolism develops after initiating therapy with Estradiol transdermal system, treatment should be immediately discontinued.

#### 4.4.1.1.6 Breast cancer

Randomised controlled trials and epidemiological studies have reported an increased risk of breast cancer in women taking HRT. Women using combined estrogen-progestogen HRT had a possibly higher risk than women who used unopposed estrogens. The excess risk of breast cancer increases with the duration of intake of combined estrogen-only and combined estrogen-progestogen HRT.

There is evidence arising from the WHI continuous combined study (see subsection Cardiovascular disease) which shows an absolute excess risk of invasive breast cancer of 8 additional cases per 10,000 person-years (38 versus 30) in the HRT-treated women and a relative risk of 1.26.

In a meta-analysis of 51 epidemiological studies conducted between the 1970s and the early 1990s, the cumulative incidence of breast cancer in non-users of HRT between the ages of 50 and 70 is about 45 per 1000 women. The cumulative excess numbers of cases of breast cancer diagnosed per 1000 women who began use of HRT between the ages of 50 and 70, and used it for 5, 10 or 15 years, is estimated to be 2, 6, and 12, respectively.

The number of additional cases of breast cancer is broadly similar among women who start HRT between the ages of 45 and 65 regardless of their age at the start of treatment.

The excess risk seems to return to baseline in the course of about five years following cessation of treatment.

For transdermal estrogen-only and estrogen-progestogen combined HRT products, no large randomised clinical trials to date have assessed the HRT-associated risk of breast cancer. Therefore there are no data to support the conclusion that the frequency of breast cancer is different with Estradiol transdermal system.

Women should be advised that changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices and adapted to the clinical needs of the individual woman.

Unopposed estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of a progestogen to estrogen replacement therapy is recommended in women who have undergone hysterectomy and who are known to have residual endometriosis.

#### 4.4.1.1.7 Endometrial cancer

The risk of endometrial cancer in users of unopposed estrogens who have an intact uterus is greater than in non-users and appears to depend on the duration of treatment and the estrogen dose. The greatest risk appears to be associated with prolonged use. It has been shown that adequate concomitant progestogen therapy lowers the incidence of endometrial hyperplasia and therefore the potential risk of endometrial carcinoma associated with prolonged use of estrogen therapy.

Estrogens, regardless of their origin, increase the risk of endometrial cancer. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

In all cases of undiagnosed persistent vaginal bleeding or spotting, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out abnormality and treatment should be re-evaluated.

#### 4.4.1.1.8 Ovarian cancer

The randomised placebo-controlled WHI (Women’s Health Initiative) estrogen plus progestin sub-study reported a statistically non-significant increased risk of ovarian cancer after an average follow-up of 5.6 years. Epidemiological evidence from a meta-analysis suggests an increased risk of ovarian cancer in women taking opposed and unopposed estrogens that becomes apparent within 5 years of use and slowly diminishes over time after discontinuation.

#### 4.4.1.1.9 Dementia

In a randomised placebo-controlled ancillary study of the WHI, the Women's Health Initiative Memory Study (WHIMS), women aged 65 and older (average age 71) treated with oral CEE and MPA for an average follow-up of 4 years were reported to have a two-fold increase in the risk of developing probable dementia. The absolute excess risk of probable dementia was 23 additional cases per 10,000 person-years (45 versus 22) in CEE/MPA treated women and the relative risk was 2.05.

In a randomised, placebo-controlled, estrogen alone ancillary study of the WHI (WHIMS), the absolute excess risk of probable dementia after an average follow-up of 5.2 years was 12 additional cases per 10,000 person-years (37 versus 25) in CEE treated women and the relative risk was 1.49, which did not reach statistical significance ($p = 0.18$) compared to placebo.

Since both sub-studies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women.

For transdermal estrogen-only or estrogen-progestogen combined products, no large randomised clinical trials have assessed the HRT-associated risk of probable dementia to date. Therefore there are no data to support the conclusion that the frequency of probable dementia is different with Estradiol transdermal system.

#### 4.4.1.1.10 Severe anaphylactic/anaphylactoid reactions and angioedema

Cases of anaphylactic/anaphylactoid reactions, which developed anytime during the course of estradiol treatment and required emergency medical management, have been reported in the post marketing setting. Involvement of skin (utricaria, pruritus, swelling of the face, throat, lips, tongue, skin and periorbital edema) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) has been noted.

Angioedema requiring medical intervention involving eye/eyelid, face, larynx, pharynx, tongue and extremity (hands, legs, ankles, and fingers) with or without urticaria has occurred in the post marketing experience of using estradiol. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop angioedema after treatment with estradiol should not receive Estradiol transdermal system again.

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

#### 4.4.1.1.11 Precautions prior to initiation of Estradiol transdermal system therapy

Before initiating or re-instituting HRT, a complete personal and family medical history, and an appropriate physical (including pelvic and breast) examination should be performed (see Contraindications and Warnings and Precautions).

Consideration should be given to the lowest dose and the shortest duration of use.

Hysterectomized women who require postmenopausal hormone replacement therapy should receive estrogen-only replacement therapy unless otherwise indicated (e.g. endometriosis).

Caution is advised when risk factors for estrogen-dependent tumours (e.g. first-degree blood relatives who have ever had breast cancer) are present.

Women should be advised that Estradiol transdermal system is not a contraceptive nor will it restore fertility.

#### 4.4.1.1.12 Monitoring during Estradiol transdermal system therapy

During treatment, periodic check-ups of a nature and frequency adapted to the individual woman are recommended. A careful appraisal of the risks and benefits should be undertaken over time in women treated with HRT and the need for HRT should be re-evaluated periodically.

If any of the following conditions are present or have occurred previously (including during pregnancy or a previous hormone treatment), the woman should be closely monitored, in particular: leiomyoma (uterine fibroids) or endometriosis, thromboembolic disorders, heart failure, hypertension, hepatic disorders (e.g. liver adenoma), renal disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, endometrial hyperplasia, epilepsy, asthma, otosclerosis, gallbladder disease, estrogen-related jaundice and pruritus.

It should be taken into account that these conditions may recur or be aggravated during treatment with estrogens.

If worsening of any of the above mentioned conditions is diagnosed or suspected during HRT, the benefits and risks of HRT should be reassessed on an individual basis.

Estrogens may cause fluid retention and therefore women with cardiac or renal dysfunction should be carefully monitored.

Women with hypertriglyceridaemia should be monitored closely during HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oral estrogen therapy in these women.

Although observations to date suggest that estrogens, including transdermal estradiol, do not impair carbohydrate metabolism, diabetic women should be monitored during initiation of therapy until further information is available.

Thyroid function should be monitored regularly in patients who require thyroid hormone replacement therapy and who are also taking estrogen in order to ensure that thyroid hormone levels remain within an acceptable range.

#### 4.4.1.1.13 Discontinuation of Estradiol transdermal system therapy

Therapy should be discontinued in the following situations: jaundice or deterioration of liver function, a significant increase in blood pressure, new onset of migraine-type headache and pregnancy, or if a condition described under Contraindications develops.

When Estradiol transdermal system therapy is combined with cyclic progestogen administration, there are often occurrences of breakthrough bleeding and spotting during the initial months of treatment.

In all cases of undiagnosed persistent or irregular vaginal bleeding, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out abnormality and the treatment should be re-evaluated.

## 4.5 Interaction With Other Medicinal Products And Other Forms Of Interaction

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

Estradiol is predominantly metabolized by CYP3A4; concomitant administration of inhibitors of CYP3A4 such as ketoconazole, erythromycin or ritonavir may therefore result in an increase of approximately 50% in estradiol exposure.

Caution should be used if the woman is receiving protease inhibitors (e.g. ritonavir and nelfinavir), which are known as strong inhibitors of cytochrome P450 enzymes, and by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Effect of HRT with estrogens on other medicinal products

Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, concomitant administration of lamotrigine with estradiol has been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may lead to a reduction in effectiveness among people taking both medicinal products together.

Herbal preparations containing St. John's wort (*Hypericum perforatum*) may induce the metabolism of estrogens and progestogens.

Clinically, increased metabolism of estrogens and progestogens may lead to decreased effects and changes in the uterine bleeding profile.

With transdermal HRT administration, the first-pass effect in the liver is avoided and thus transdermally applied estrogens may be less affected by enzyme inducers than oral hormones.

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

## 4.6 FERTILITY, PREGNANCY AND LACTATION

#### 4.6.1.1.1 Women of Child-bearing Potential and Contraceptive Measures

Not applicable.

#### 4.6.1.1.2 Pregnancy

Estradiol transdermal system must not be used during pregnancy. Both estrogens and progestogens may cause foetal harm when administered to a pregnant woman.

#### 4.6.1.1.3 Breast-feeding

Estradiol transdermal system must not be used while breastfeeding.

#### 4.6.1.1.4 Fertility

Not applicable.

## 4.7 Effects on ability to drive and use machines

No known effects.

## 4.8 Undesirable effects

Adverse drug reactions from multiple sources including clinical trials and post-marketing experience (Table 1) are listed according to the system organ class in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, the most frequent first. Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness. In addition the corresponding frequency using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports and not known.

### 4.8.1.1 Table 1

| | | |
|---|---|---|
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | | |
| | Uncommon: | Breast cancer. |
| **Immune system disorders** | | |
| | Not known [(1)]: | Anaphylactic reaction, anaphylactoid reaction, hypersensitivity. |
| **Psychiatric disorders** | | |
| | Common: | Depression. |
| | Not known [(1)]: | Nervousness, affect liability |
| **Nervous system disorders** | | |
| | Common: | Headache, Migraine, dizziness. |
| **Cardiac disorders** | | |
| | Not known | Embolism, hypertension |
| **Gastrointestinal disorders** | | |
| | Common: | Nausea, abdominal pain, abdominal distension. |
| | Uncommon: | Vomiting. |
| | Not known [(1)]: | Cholelithiassis, liver function tests abnormal, diarrhoea |
| **Skin and subcutaneous tissue disorders** | | |
| | Uncommon: | Alopecia, hirsutism. |

| | |
|---|---|
| Not known[(1)]: | Angioedema, erythema nodosum, erythema multiforme, rash generalised, pruritus generalised, urticaria, contact dermatitis, chloasma. |

**Musculoskeletal and connective tissue disorder**

| | |
|---|---|
| Not known | Back pain, pain in extremities |

**Reproductive system and breast disorders**

| | |
|---|---|
| Very common: | Breast tenderness. |
| Common: | Menstrual disorders (changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow), metrorrhagia, cervical discharge, breast enlargement. |
| Uncommon: | Genital candidiasis, uterine leiomyoma. |
| Not known [(1)]: | Endometrial hyperplasia, breast discomfort, breast pain, dysmenorrhoea, fibrocystic breast disease, breast discharge. |

**General disorders and administration site conditions**

| | |
|---|---|
| Very common: | Application site reaction[(2)] (at the patch application site, observed after removing the patch by peeling from the skin). |
| Common: | Weight fluctuation, oedema, pruritus and rash (around the application site). |
| Uncommon: | Libido increased or decreased. |

*(1) Reported in post-marketing experience.*

*(2) Application site reactions includes localized bleeding, bruising, burning, discomfort, dryness, eczema, edema, erythema, inflammation, irritation, pain, papules, paraesthesia, pruritus, rash, skin discolouration, skin pigmentation, swelling, urticaria, and vesicles*

The following adverse reactions have been reported in association with some estrogen-progestogen treatments:

- Estrogen-dependent neoplasms, benign and malignant, e.g. endometrial cancer,
- Embolism venous, e.g. deep leg or pelvic venous thrombosis and pulmonary embolism,
- Cerebrovascular accident,
- Myocardial infarction,
- Cholestatic jaundice,
- Gallbladder disease,

- Aggravation of porphyria,
- Dementia
- Chorea,
- Contact lens intolerance (dry eyes and tear film compositions changes),
- Purpura,
- Carbohydrate tolerance decreased.

#### 4.8.1.1.1 Ovarian Cancer

Use of estrogen-only and or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see warnings and precautions).

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.

#### 4.8.1.1.2 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

Acute overdosage is unlikely due to the mode of administration. The most common symptoms of overdosage in clinical use are breast tenderness and/or vaginal bleeding. If such symptoms occur, a reduction in dosage should be considered. The effects of overdosage can be rapidly reversed by removal of the patch.

**For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).**

# 5 PHARMACOLOGICAL PROPERTIES

#### 5.1.1.1.1 Pharmacotherapeutic Group and ATC

Pharmacotherapeutic group: Estrogens

ATC code G03CA03

#### 5.1.1.1.2 Mechanism of Action

### 5.1.2 Pharmacodynamic properties (PD)

The active substance in Estradiol transdermal system, 17-beta-estradiol, is chemically and biologically identical to the endogenous human 17-beta-estradiol and is classified as a natural estrogen. It compensates for the decreasing estrogen production in menopausal women and

alleviates menopausal symptoms. Estradiol prevents bone loss after the menopause or after an ovariectomy.

#### 5.1.2.1.1 Clinical Studies

Estradiol transdermal system is an established product. No new recent clinical studies are available.

## 5.2 Pharmacokinetic properties

Transdermal administration of estradiol achieves therapeutic plasma concentrations using a lower total dose of estradiol than required with oral administration. Plasma levels of estrone and estrone conjugates are also lower with the transdermal route.

Estradiol is more than 50% bound to plasma proteins such as sex-hormone-binding globulin and albumin. The sulfate and glucuronide esters along with a small proportion of estradiol and several other metabolites are excreted in the urine. Only a small amount is excreted in faeces.

In studies in postmenopausal women with application of 2.5, 3.75, 5 and 10 $cm^2$ Estradiol transdermal system patches, average peak estradiol serum levels ($C_{max}$) were approximately 25 pg/mL, 35 pg/mL, 50-55 pg/mL and 95-105 pg/mL, respectively. Linear pharmacokinetics have been demonstrated for estradiol following transdermal administration.

Since estradiol has a short half-life (approximately one hour), serum concentrations of estradiol and estrone returned to baseline values within 24 hours following removal of the patch.

At steady state, after repeated applications of 5 $cm^2$ (50 micrograms/day) Estradiol transdermal system patches, estradiol $C_{max}$ and $C_{min}$ values (57 and 28 pg/mL, respectively) were similar to those in the single application study, while estrone $C_{max}$ and $C_{min}$ values were lower (42 and 31 pg/mL, respectively).

## 5.3 Preclinical safety data

The toxicity profile of estradiol is well established. Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Adhesive matrix: acrylic adhesive, silicone adhesive, oleyl alcohol, dipropylene glycol and povidone.

Backing layer: ethylene vinyl acetate/polyethylene copolymer and vinylidene chloride/vinyl chloride copolymer.

Release liner: Fluoropolymer-coated polyester.

## 6.2 Incompatibilities

No incompatibilities with other medicaments are known.

## 6.3 Shelf life

2 years.

## 6.4 Special precautions for storage

Store at or below 25ºC. Do not freeze. Protect from light.

The patches should not be stored once opened but should be applied immediately upon removal from the protective sachet.

Estradiol transdermal system patches must be kept out of the reach and sight of children.

## 6.5 Nature and contents of container

Packs contain 8 patches. Each Estradiol transdermal system patch is individually sealed in an aluminium laminate sachet.

* Not all presentations are available in New Zealand

## 6.6 Special precautions for disposal and other handling

See section 4.2.

After use, Estradiol transdermal system patch should be folded (adhesive surfaces pressed together) and discarded in such a way as to keep them out of the reach and sight of children.

# 7 MEDICINE SCHEDULE

Prescription Medicine

# 8 SPONSOR

Sandoz New Zealand Limited

12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

# 9 DATE OF FIRST APPROVAL

30 May 2024

# 10 DATE OF REVISION OF THE TEXT

31 July 2024

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 4.4, 4.8, 5.1 | Minor editorial changes |
| 4.5 | Addition of drug interaction with lamotrigine |