ESTRADOT®

Oestradiol transdermal patch

WARNING

Oestrogens with or without progestogens should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated oestrogens (0.625 mg) relative to placebo (See CLINICAL TRIALS and PRECAUTIONS).

The WHI study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (See CLINICAL TRIALS and PRECAUTIONS).

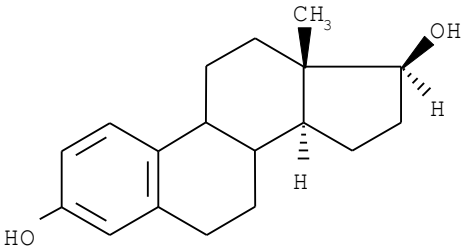
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated oestrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (See CLINICAL TRIALS and PRECAUTIONS).

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

NAME OF THE MEDICINE

The active ingredient is oestradiol or oestra-1,3,5 (10)-triene-3, 17beta-diol, the major oestrogenic hormone produced by the human ovary.

Chemical Structure:



oestradiol

CAS: 50-28-2

DESCRIPTION

- Estradot is available in five sizes:
- Estradot 25: 2.5 cm^2 patch containing 0.39 mg oestradiol (as hemihydrate) with a nominal *in vivo* release rate of 25 micrograms oestradiol per day.
- Estradot 37.5: 3.75 cm^2 patch containing 0.585 mg oestradiol (as hemihydrate) with a nominal *in vivo* release rate of 37.5 micrograms oestradiol per day.
- Estradot 50: 5 cm^2 patch containing 0.78 mg oestradiol (as hemihydrate) with a nominal *in vivo* release rate of 50 micrograms oestradiol per day.
- Estradot 75: 7.5 cm^2 patch containing 1.17 mg oestradiol (as hemihydrate) with a nominal *in vivo* release rate of 75 micrograms oestradiol per day.
- Estradot 100: 10 cm^2 patch containing 1.56 mg oestradiol (as hemihydrate) with a nominal *in vivo* release rate 100 micrograms oestradiol per day.

Excipients: Dipropylene glycol, povidone and oleyl alcohol. Proprietary ingredients: Gelva RA-788 acrylic adhesive, BIO-PSA 7-4502 silicone adhesive, Dow BLF 2050 non-removable backing layer and Scotchpak 1022 removable release liner.

PHARMACOLOGY

Pharmacodynamics

The active substance in Estradot, 17beta-oestradiol, is chemically and biologically identical to the endogenous human 17beta-oestradiol and is classified as a natural oestrogen. It compensates for the decreasing oestrogen production in menopausal women and alleviates menopausal symptoms. Oestradiol prevents bone loss after the menopause or after an ovariectomy. When Estradot is used for the short-term relief of menopausal symptoms, it will provide a concomitant preventative effect in reducing bone mineral density loss.

Pharmacokinetics

Absorption

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

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

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

A comparative, multiple dose, cross-over bioequivalence study in 30 healthy post-menopausal women administered Estradot 50 or Menorest 50 for four 84-hour dosing periods with a 7-day washout period between treatments demonstrated that, at steady state, the $AUC_{(0-84h)}$ and C_{max} values for oestradiol were comparable for the Estradot 50 microgram/day patch and the Menorest 50 microgram/day patch.

Distribution

Oestradiol is more than 50% bound to plasma proteins such as sex hormone binding globulin and albumin. Only 2% is free and biologically active.

Metabolism

Once systemically absorbed, transdermally applied oestradiol is metabolised in the same way as the endogenous hormone. Oestradiol is metabolised primarily in the liver to oestrone, then later to oestriol, epioestriol and catechol oestrogens, which are then conjugated to sulphates and glucuronides. Cytochrome 450 isoforms CYP1A2 and CYP3A4 catalyze the hydroxylation of oestradiol forming oestriol. Oestriol is glucuronidated by UGT1A1 and UGT2B7 in humans. Oestradiol metabolites are subject to enterohepatic circulation.

Elimination

The sulfate and glucuronide esters along with a small proportion of oestradiol and several other metabolites are excreted in the urine. Only a small amount is excreted in faeces.
Since oestradiol has a short half-life (approximately one hour), serum concentrations of oestradiol and oestrone returned to baseline values within 24 hours following removal of the patch.

CLINICAL TRIALS

There are no clinical efficacy and safety data available for Estradot. However, the development of Estradot was based on the essential similarity of this product to Menorest (oestradiol) patches, for which there are clinical data.

Study 305: A two-year, randomised, double blind, placebo-controlled study was conducted with Menorest in post-menopausal women. 242 (intent-to-treat) women received Menorest (25, 50 or 75 microgram/day) or placebo patches applied twice weekly for a 28 day cycle. In women with an intact uterus, dydrogesterone tablets were taken with Menorest, or placebo tablets with the placebo patch, for the last 14 days of the cycle. Changes in postmenopausal symptoms were evaluated as a secondary efficacy variable. All three active treatments produced a statistically significant decrease in the severity of hot flushes when compared to placebo. The difference between each active treatment group and placebo at 3 months was statistically significant ($p \leq 0.01$) and continued throughout the study. The severity of sweating was also decreased in the active treatment groups compared to placebo at 3 months and was maintained for the duration of the study ($p<0.027$ for all active treatment groups compared to baseline values).

Clinical data are not available for the elderly post-menopausal population.

Women's Health Initiative (WHI) Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral conjugated oestrogens (CE) 0.625 mg/day alone or the use of a continuous combined regimen of conjugated oestrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day (CE + MPA) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE alone or CE + MPA on menopausal symptoms.

The oestrogen alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of oestrogen alone in predetermined primary endpoints. Results of the oestrogen alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15% Black, 6.1% Hispanic), after an average follow-up of 6.8 years are presented in Table 1.

TABLE 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN ALONE SUBSTUDY OF WHI[a]

Event[c]	Relative Risk* CE alone vs Placebo at 6.8 Years (95% CI)	Placebo n = 5429	CE alone n = 5310
		Absolute Risk per 10,000 Women-years	
CHD events	0.91 (0.75-1.12)	54	49
Non-fatal MI	*0.89 (0.70-1.12)*	*41*	*37*
CHD death	*0.94 (0.65-1.36)*	*16*	*15*
Invasive breast cancer	0.77 (0.59-1.01)	33	26
Stroke	1.39 (1.10-1.77)	32	44
Pulmonary embolism	1.34 (0.87-2.06)	10	13
Colorectal cancer	1.08 (0.75-1.55)	16	17
Hip fracture	0.61 (0.41-0.91)	17	11
Death due to other causes than the events above	1.08 (0.88-1.32)	50	53
Global Index[b]	1.01 (0.91-1.12)	190	192
Deep vein thrombosis[c]	1.47 (1.04-2.08)	15	21
Vertebral fractures[c]	0.62 (0.42-0.93)	17	11
Total fractures[c]	0.70 (0.63-0.79)	195	139

a: adapted from JAMA, 2004; 291:1701-1712

b: a subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

c: not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CEE alone were 12 more strokes while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See BOXED WARNING and PRECAUTIONS.)

The oestrogen plus progestogen substudy was also stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". Results of the oestrogen plus progestogen substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 2.

TABLE 2. RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN PLUS PROGESTOGEN SUBSTUDY OF WHI[a]			
Event[c]	Relative Risk CE + MPA vs Placebo at 5.2 Years (95% CI*)	Placebo n = 8102	CE + MPA n = 8506
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index [c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

a: adapted from JAMA, 2002; 288:321-333

b: includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

c: a subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

d: not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the WHI "global index", the absolute excess risks per 10,000 women-years in the group treated with CE + MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See BOXED WARNING and PRECAUTIONS)

Women's Health Initiative Memory Study.

The oestrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45% were age 65 to 69 years, 36% were 70 to 74 years, and 19% were 75 years of age and older) to evaluate the effects of conjugated oestrogens (CE) 0.625 mg/day alone on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the oestrogen alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the oestrogen alone group was 1.49 (95% CI, 0.83 to 2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNING and PRECAUTIONS, Dementia and Use in Geriatrics.)

The oestrogen plus progestogen WHIMS substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of oral conjugated oestrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day (CE + MPA) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the oestrogen/progestogen group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNING and PRECAUTIONS, Dementia and Use in Geriatrics.)

INDICATIONS

Short term treatment of symptoms of oestrogen deficiency due to the menopause, whether natural or surgically induced.

In women with an intact uterus, oestrogen should always be opposed by progestogen in an adequate dosage regimen to ensure secretory transformation of the endometrium at regular intervals (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

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

CONTRAINDICATIONS

- Known, past or suspected carcinoma (or history of carcinoma) of the breast
- Known or suspected carcinoma of the endometrium or other oestrogen-dependent neoplasia
- Undiagnosed abnormal vaginal bleeding
- Severe hepatic impairment
- Active venous thromboembolism [VTE] (e.g. deep venous thrombosis, pulmonary embolism), known thrombophilic or thromboembolic disorders (e.g. thrombophlebitis),

arterial thromboembolic disease (e.g. coronary heart disease, stroke), or a documented history of these conditions
- Porphyria
- Known or suspected pregnancy
- Breast-feeding
- Non-hysterectomised women unless on concomitant progestogen therapy
- Known hypersensitivity to oestrogens or any other component of the Estradot transdermal patch.

PRECAUTIONS

The benefits and risks of oestrogen / progestogen therapy must always be carefully weighed, including consideration of the emergence of risks as therapy continues.

1. Cardiovascular disorders

Oestrogen and oestrogen/progestogen therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, oestrogen/progestogen therapy should be discontinued immediately.

Risk factors for arterial vascular disease (e.g. hypertension, diabetes mellitus, tobacco use, hypercholesterolaemia and obesity) and/or venous thromboembolism (e.g. personal history or family history of VTE, obesity and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke

In the oestrogen alone substudy of the Women's Health Initiative (WHI) study, an increased risk of stroke was observed in women receiving conjugated estrogens (CE) 0.625 mg per day compared to women receiving placebo (44 vs 32 per 10,000 women-years). The increase in risk was observed in year one and persisted. (See CLINICAL TRIALS)

In the oestrogen plus progestogen substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE + MPA (conjugated estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same oestrogen plus progestogen substudy of WHI, an increased risk of stroke was observed in women receiving CE + MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with CE + MPA demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE + MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE + MPA -treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE + MPA group and the placebo group in HERS, HERS II, and overall.

b. Venous thromboembolism (VTE)

In the oestrogen alone substudy of the Women's Health Initiative (WHI) study, an increased risk of deep vein thrombosis was observed in women receiving CE compared to placebo (21 vs 15 per 10,000 women-years). The increase in VTE risk was observed during the first year. (See CLINICAL TRIALS.)

In the oestrogen plus progestogen substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE + MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE + MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, oestrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation.

Generally recognised risk factors for VTE include a personal history (see CONTRAINDICATIONS), a family history of thromboembolic disease (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe 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 patients in whom this diagnosis is confirmed, the use of Estradot is contraindicated.

Patients 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 VTE develops after initiating HRT, the drug should be discontinued.

2. Malignant neoplasms

a. Endometrial cancer

The use of unopposed oestrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed oestrogen users with an intact uterus is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with the use of oestrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after oestrogen therapy is discontinued.

Clinical surveillance of all women taking oestrogen/progestogen combinations 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. There is no evidence that the use of natural oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose. Adding a progestogen to postmenopausal oestrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer

In some studies, the use of oestrogens and progestogens by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomised clinical trial providing information about this issue is the Women's Health Initiative (WHI) trial of oestrogen plus progestogen (see CLINICAL TRIALS). The results from observational studies are generally consistent with those of the WHI clinical trial.

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took oestrogen plus progestogen. Observational studies have also reported an increased risk for oestrogen/progestogen combination therapy, and a smaller increased risk for oestrogen alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with oestrogen/progestogen combination therapy as compared to oestrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different oestrogens or among different oestrogen/progestogen combinations, doses, or routes of administration.

In the WHI trial of oestrogen plus progestogen, 26% of the women reported prior use of oestrogen alone and/or oestrogen/progestogen combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast

cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for oestrogen plus progestogen compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the oestrogen plus progestogen group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of oestrogens alone or oestrogens plus progestogens compared to never users, while the oestrogen plus progestogen sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

The use of oestrogen plus progestogen has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

3. Dementia

In the oestrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomised women aged 65 to 79 years was randomised to conjugated estrogens (CE) 0.625 mg/day or placebo. In the oestrogen plus progestogen WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomised to CE + MPA or placebo.

In the oestrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the oestrogen alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone versus placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years.

In the oestrogen plus progestogen substudy, after an average follow-up of 4 years, 40 women in the oestrogen plus progestogen group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for oestrogen plus progestogen versus placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for CE + MPA versus placebo was 45 versus 22 cases per 10,000 women-years.

Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNING and PRECAUTIONS, Use in Geriatrics.)

4. Severe anaphylactic/anaphylactoid reactions and angioedema

Cases of anaphylactic/anaphylactoid reactions, which developed anytime during the course of oestradiol treatment and required emergency medical management, have been reported in the post marketing setting. Involvement of skin (urticaria, pruritus, swelling of the face, throat, lips, tongue, skin and periorbital oedema) 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 oestradiol. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop angioedema after treatment with oestradiol should not receive Estradot again.

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

5. Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported.

6. Hypercalcaemia

Oestrogen administration may lead to severe hypercalcaemia in patients with breast cancer and bone metastases. If hypercalcaemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

7. Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving oestrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, oestrogens should be discontinued.

8. General precautions

a. ***Addition of a progestogen when a woman has not had a hysterectomy.***

Studies of the addition of a progestogen for 10 or more days of a cycle of oestrogen administration, or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestogens with oestrogens compared with oestrogen-alone regimens. These include a possible increased risk of breast cancer and impairment of glucose tolerance.

b. ***Elevated blood pressure***

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to oestrogens. In a large, randomised, placebo-controlled clinical trial, a generalised effect of oestrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with oestrogen use.

c. ***Hypertriglyceridaemia***

In patients with pre-existing hypertriglyceridaemia, oestrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

d. ***Impaired liver function and past history of cholestatic jaundice***

Oestrogens may be poorly metabolised in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

e. ***Hypothyroidism***

Oestrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving oestrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

f. ***Fluid retention***

Because oestrogens/progestogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when oestrogens are prescribed.

g. ***Hypocalcaemia***

Oestrogens should be used with caution in individuals with severe hypocalcaemia.

h. ***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 WHI trial suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see ‘ADVERSE EFFECTS’).”

i. ***Exacerbation of endometriosis***

Endometriosis may be exacerbated with administration of oestrogen therapy.

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with oestrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestogen should be considered.

j. ***Exacerbation of other conditions***

Oestrogen therapy may cause an exacerbation of asthma, diabetes mellitus with or without vascular involvement), epilepsy, migraine or severe headache, porphyria, systemic lupus erythematosus and hepatic hemangiomas and should be used with caution in women with these conditions.

The patient should also be closely monitored if any of the following conditions are present or have occurred previously (including during pregnancy or a previous hormone treatment): leiomyoma (uterine fibroids), hepatic disorders (e.g. liver adenoma), cholelithiasis, heart failure, past endometriosis, endometrial hyperplasia, otosclerosis, gallbladder disease, oestrogen-related jaundice and pruritus.

It should be taken into account that these conditions may recur or be aggravated during treatment with oestrogens. If worsening of any of the above conditions is diagnosed or suspected during HRT, the benefits and risks of continuing HRT should be reassessed.

Treatment with HRT should be stopped in the following situations: an increase in epileptic seizures, jaundice or deterioration in liver function, a significant increase in blood pressure, new onset of migraine type headache, pregnancy or if a condition described under CONTRAINDICATIONS develops.

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

k. ***Contact sensitisation***

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

l. Patient monitoring

Estradot, like any other form of sex-hormone therapy, should only be prescribed or reinstated after a thorough general medical and family history and a gynaecological examination, including a cervical smear, and endometrial abnormalities and breast cancer have been ruled out. In patients receiving prolonged treatment, these examinations should be repeated at least once a year.

Regular examination of the breasts is desirable. 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.

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.

Women should be advised that Estradot is not a contraceptive, nor will it restore fertility.

Effects on ability to drive and use machines
No known effects.

Use in patients with renal and / or hepatic impairment
No studies were performed in patients with renal and hepatic impairment.
All oestrogen preparations are contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS).

Use in children
Estradot should not be used in children.

Use in Geriatrics
Of the total number of subjects in the oestrogen alone substudy of the Women's Health Initiative (WHI) study, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

In the oestrogen alone substudy of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to conjugated estrogens (CE) 0.625 mg/day or placebo. In the oestrogen alone group, after an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 (95% CI 0.83-2.66).

Of the total number of subjects in the oestrogen plus progestogen substudy of the Women's Health Initiative study, 44% (n=7,320) were 65 years and over, while 6.6% (n=1,095) were 75 years and over. There was a higher relative risk (CE + MPA vs placebo) of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.
In the oestrogen plus progestogen substudy of WHIMS, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomised to CE + MPA or placebo. In the oestrogen plus progestogen group, after an average follow-up of 4 years, the relative risk (CE + MPA versus placebo) of probable dementia was 2.05 (95% CI 1.21-3.48).

Pooling the events in women receiving CE or CE + MPA in comparison to those in women on placebo, the overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNING and PRECAUTIONS, Dementia.)

Carcinogenesis, mutagenesis, impairment of fertility
Unopposed oestrogen therapy in women with intact uteri is associated with an increased risk of endometrial carcinoma, particularly with prolonged use. An increased risk of tumours in oestrogen-sensitive target organs, such as breast and ovary, is also associated with prolonged oestrogen therapy (see PRECAUTIONS).

Long-term animal studies of natural and synthetic oestrogens have shown an increased incidence of carcinomas in the breast, uterus, cervix, vagina, testis and liver.

There is limited evidence available in the literature suggesting that oestradiol may be weakly genotoxic. Genotoxicity assays with oestradiol have revealed no evidence of gene mutation in bacterial or mammalian cells, but there is 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 oestradiol in human lymphocyte cultures. Importantly, there was no evidence of micronuclei formation in rodent bone marrow micronucleus assays.

Use in Pregnancy (Category B1)
Oestrogens must not be used during pregnancy (see CONTRAINDICATIONS). Both oestrogens and progestogens may cause foetal harm when administered to a pregnant woman.

Use in Lactation
Oestrogens must not be used while breast-feeding (see CONTRAINDICATIONS).

INTERACTIONS WITH OTHER MEDICINES

The metabolism of oestrogens 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. phenobarbitone, phenytoin, carbamazepine), meprobamate, phenylbutazone and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Oestradiol 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 patient 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.

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

Clinically, increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile. With transdermal HRT administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens may be less affected by enzyme inducers than oral hormones.

Interference with laboratory tests:
Some laboratory tests may be influenced by oestrogen therapy, such as tests for glucose tolerance or thyroid function.

ADVERSE EFFECTS

Adverse reactions from multiple sources including clinical trials (Table 3) and post-marketing experience 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.

Table 3

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	Nervousness, affect liability
Nervous system disorders		
	Common:	Headache, migraine, dizziness.
Cardiac disorders		
	Not known [(1)]:	Embolism, hypertension
Gastrointestinal disorders		
	Common:	Nausea, abdominal pain, abdominal distension.
	Uncommon:	Vomiting.
	Not known [(1)]:	Cholelithiassis, liver function tests abnormal, diarrhoea
Musculoskeletal and connective tissue disorder		
	Not known [(1)]:	Back pain, pain in extremity
Skin and subcutaneous tissue disorders		
	Uncommon:	Alopecia, hirsutism.
	Not known[(1)]:	Angioedema, erythema nodosum rash generalised, pruritus generalised, erythema multiforme, urticaria, contact dermatitis, chloasma.
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 change, oedema, pruritus and rash (around the application site).
	Uncommon:	Libido increased or decreased.

[1] Reported in post-marketing experience

[2] Application site reactions include 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 oestrogen-progestogen treatments:

- oestrogen-dependent neoplasms, benign and malignant (e.g. endometrial cancer)
- Embolism venous thromboembolism (e.g. deep leg or pelvic venous thrombosis and pulmonary embolism)
- Cerebrovascular accident
- myocardial infarction
- cholestatic jaundice
- gallbladder disease
- aggravation of porphyria (see CONTRAINDICATIONS).
- dementia
- chorea
- contact lens intolerance (dry eyes and tear film compositions changes)
- purpura
- chloasma
- carbohydrate tolerance decreased

Ovarian cancer

Use of oestrogen-only or combined oestrogen-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 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.

DOSAGE AND ADMINISTRATION

The lowest effective dose should be used and consideration should be given to the shortest duration of use. A careful appraisal of the risks and benefits should be undertaken over time in women treated with HRT and the need for treatment re-evaluated periodically. Treatment with either oestrogens alone or oestrogen-progestogen combined HRT therapy should only be continued as long as the benefits outweigh the risks for the individual (see PRECAUTIONS).

Dosage

Treatment is usually initiated with an Estradot 50 patch. Depending on the clinical response the dose should then 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 should be decreased. Maintenance therapy must always be at the lowest effective dose.

General Instructions

Estradot is administered as continuous therapy (uninterrupted application twice weekly).

In women with an intact uterus, Estradot should be combined with a progestogen approved for addition to oestrogen 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 oestrogens or in women switching from another oestradiol transdermal therapy, treatment with Estradot may be initiated at any convenient time. In women who are currently taking oral oestrogens, treatment with Estradot should be initiated one week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear within one week.

Method of Administration

The adhesive side of Estradot should be placed on a clean, dry area of the abdomen.

Estradot should be replaced twice weekly (i.e. every 3 to 4 days). (It's easier to remember if the patch is changed on the same days, e.g. Monday morning and Thursday evening so that each patch is worn for 3½ days).

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. Interruption of treatment may increase the likelihood of recurrence of symptoms.

- **Estradot must not be applied to the breasts.**
- **The patch should not be affixed twice in succession to the same site.**
- **The applied patch should not be directly exposed to sunlight or worn in a solarium.** Immediately after removal from the pouch, Estradot should be applied to skin sites that will be covered by clothes.
- **The patch must not be cut or torn.**

OVERDOSAGE

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.

Safety note concerning children
Estradot should be kept out of the reach of children both before and after use. Used patches contain residual oestradiol.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Estradot is available in five sizes: Estradot 25, 37.5, 50, 75 and 100, in packs of 8 patches (and 2 patches – sample pack).
Each Estradot patch is individually sealed in an aluminium laminate sachet.

Storage: Store below 25°C. Protect from light and freezing.

NAME AND ADDRESS OF THE SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Ltd
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54 Waterloo Road
Macquarie Park NSW 2113
® = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

Schedule 4 - Prescription Only Medicine Only

DATE OF FIRST INCLUSION IN THE ARTG

05 February 2004

DATE OF MOST RECENT AMENDMENT

04 May 2017
