# ESTRADERM MX

**oestradiol, transdermal patch**

<table>
<thead>
<tr>
<th>WARNING</th>
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</table>

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, 17β-diol, the major oestrogenic hormone produced by the human ovary.

Chemical Structure:

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HO
H
CH3

HO
H

Oestradiol

CAS: 50-28-2
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DESCRIPTION

Estraderm MX contains 0.75 mg, 1.5 mg, 2.25 mg or 3.0 mg oestradiol in a transdermal therapeutic system. The systems also contain the excipients: isopropyl palmitate, acrylate, methacrylate, polyethylene terephthalate, ethylene/vinylacetate copolymer and a silicone coating on the inner surface of the protective release liner (discarded before use).

Estraderm MX is a thin flat multi-laminate sheet, square with rounded corners, on an oversized protective liner. A drug/adhesive matrix which is laminated to a polyester backing film is directly in contact with the skin. The active substance penetrates the skin from the adhesive and passes directly into the bloodstream for up to four days after application.

Estraderm MX 25, 50, 75 and 100 have a nominal in vivo release rate of 25, 50, 75 and 100 micrograms/24h, respectively. Estraderm MX 25, 50, 75 and 100 contain 0.75 mg, 1.5 mg, 2.25 mg and 3.0 mg oestradiol and have drug releasing areas of 11 cm², 22 cm², 33 cm² and 44 cm², respectively.

Estraderm MX is composed of three layers. Proceeding from the visible outer surface towards the inner surface, next to the skin, the layers are:

1. An impermeable, transparent backing film.
2. A drug/adhesive matrix containing oestradiol.
3. A protective liner (to be removed prior to use).

Estraderm MX overcomes the problems of the short half-life and extensive first pass metabolism of oestradiol.
**PHARMACOLOGY**

**Pharmacodynamics**
Like all steroidal hormones, oestrogens exert their metabolic effects intracellularly. In the cells of the target organs oestrogens interact with a specific receptor to form a complex which stimulates both DNA and protein synthesis. Such receptors have been identified in various organs, e.g. the hypothalamus, pituitary, vagina, urethra, uterus, breast and liver, and in osteoblasts.

Oestradiol, which in women from the menarche to the menopause is produced mainly by the ovarian follicles, is the oestrogen most active at the receptor level. After the menopause, when the ovaries have ceased to function, only a little oestradiol is still produced, i.e. from aromatisation of androstenedione and to a lesser extent of testosterone by the aromatase enzyme, yielding oestrone and oestradiol respectively. Oestrone is further transformed to oestradiol by the enzyme 17β-hydroxysteroid dehydrogenase. Both enzymes prevail in fat, liver and muscle tissue.

In many women, cessation of ovarian oestradiol production results in vasomotor and thermoregulatory instability (hot flushes), sleep disturbances, and progressive atrophy of the urogenital system. These disorders can be largely eliminated by means of oestrogen replacement therapy. Owing to the accelerated loss of bone substance induced by postmenopausal oestrogen deficiency, women may develop osteoporosis, particularly of the vertebral column, hip and wrist.

Known risk factors for postmenopausal osteoporosis include early menopause or surgical oophorectomy, prolonged secondary amenorrhoea, prolonged systemic steroid use and a family history of osteoporosis. Women especially at risk are those who are Caucasian, small boned, smokers and live a sedentary lifestyle.

Estraderm MX delivers the major oestrogenic hormone secreted by the human ovary, oestradiol, through the skin directly into the bloodstream in unchanged form. Estraderm MX raises the blood oestradiol concentrations to levels similar to those in the early to mid follicular phase of ovulation and maintains them over the application period. In the plasma the concentration ratio of oestradiol (E$_2$) to oestrone (E$_1$) undergoes a corresponding shift from between 1:5 and 1:2 to approximately 1:1, i.e. to values such as are recorded before the menopause in women with normally functioning ovaries.

Since the amount of oestradiol absorbed from Estraderm MX is similar to that absorbed from Estraderm and because Estraderm MX has a smoother concentration-time curve than Estraderm, it can be concluded that the pharmacodynamic effects described below are comparable for both types of patches.

Short term treatment with oestrogen replacement therapy perimenopausally has been shown to prevent loss of bone density. This effect has also been shown when Estraderm 100, the
transdermal oestrogen reservoir patch containing alcohol, is started as late as fifteen years after the menopause. One year treatment with Estraderm 100 prevented further loss of bone mass, without restoring it to premenopausal levels, in 32 postmenopausal women already diagnosed as having fractures (see “INDICATIONS”).

As yet there is no evidence of the minimum duration of oestrogen replacement therapy for the younger postmenopausal woman which will be effective subsequently in reducing fracture at the age of greatest fracture risk of 75 years of age.

No data are available on the effect of Estraderm MX 25 to prevent post-menopausal bone mineral density loss. Estraderm MX 25 should not be used in this indication.

Following the application of Estraderm for 28 days, no effect has been observed on the concentrations or activity of the blood coagulation factors fibrinopeptide A, high-molecular-weight fibrinogen, and antithrombin III. After this period of 28 days, transdermally administered oestradiol did not induce any change in the concentrations either of circulating renin substrate or of the sex hormone-binding, thyroxine-binding or cortisol-binding globulins. It has been found, however, that after only 3 weeks’ administration, transdermally administered oestradiol elicits a dose-dependent reduction in urinary excretion of calcium and hydroxyproline.

Administration of transdermal Estraderm to postmenopausal women for up to 3 years has been shown to reduce serum total cholesterol, low density lipo-protein (LDL-cholesterol) and triglyceride levels. Increases in high density lipoprotein (HDL-cholesterol) have been observed in some short-term studies (6 - 18 months). However, these changes have been shown in robust studies not to be of clinical benefit (see “PRECAUTIONS–Cardiovascular disorders”).

Estraderm therapy for 3 months has been shown to reduce fasting insulin levels and increase hepatic clearance.

Regardless of the route of administration, oestrogen doses required to relieve menopausal symptoms and conserve bone mass are also a potent stimulus for endometrial mitosis and proliferation. Unopposed oestrogens increase the incidence of endometrial hyperplasia and the risk of endometrial carcinoma. With 1 year of unopposed oestrogen therapy, endometrial hyperplasia has been found in up to 57 % of biopsies. Endometrial hyperplasia also occurs with unopposed transdermal oestrogen therapy. Specifically with the higher doses of Estraderm, a high rate of endometrial hyperplasia has also been observed.

**Pharmacokinetics**

Within 8 hours after application of Estraderm MX 50 to the skin, steady-state plasma oestradiol concentrations are reached and remain stable during 4 days. The mean E₂ concentration during steady-state of Estraderm MX 50 is 41 pg/mL in healthy postmenopausal women, corresponding to a mean increase of 37 pg/mL over the mean baseline value of 4 pg/mL (range 2.1 - 9.0 pg/mL). The E₂:E₁ ratio increases from a postmenopausal value of 0.3
to a value of 1.3, similar to the physiological $E_2:E_1$ ratio observed before menopause in women with normally functioning ovaries. During continuous treatment of postmenopausal patients with Estraderm MX twice weekly for 12 weeks, mean $E_2$ plasma concentrations rise by 36 pg/mL above baseline at the end of the treatment phase, without any indication that accumulation of $E_2$ levels occurs.

With Estraderm MX 25, $E_2$ plasma levels half those observed with Estraderm MX 50 are measured, and with Estraderm MX 100 plasma $E_2$ levels are slightly more than double those measured with Estraderm MX 50. A bioavailability study has provided evidence of bioequivalence between Estraderm MX 75 and Estraderm MX 25 plus Estraderm MX 50 applied simultaneously. These studies showed wide variability between subjects.

While Estraderm MX and Estraderm patches are effective, they are not strictly bioequivalent and they may not necessarily be interchangeable.

Plasma oestradiol concentrations return to the baseline value within 24 hours after removal of the system.

The elimination half-life of oestradiol in plasma is approximately 1 hour. The metabolic plasma clearance rate ranges from 650 to 900 L/(day x m²). Oestradiol is mainly metabolised in the liver. Its most important metabolites are oestriol and oestrone and their conjugates (glucuronides, sulphates); these are far less active than oestradiol. The bulk of the conjugates are excreted in the urine. Oestrogen metabolites are also subject to enterohepatic circulation.

**CLINICAL TRIALS**

**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>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk*</th>
<th>Placebo n = 5429</th>
<th>CE alone n = 5310</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>0.91 (0.75-1.12)</td>
<td>54</td>
<td>49</td>
</tr>
<tr>
<td><strong>Non-fatal MI</strong></td>
<td>0.89 (0.70-1.12)</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td><strong>CHD death</strong></td>
<td>0.94 (0.65-1.36)</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>0.77 (0.59-1.01)</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.39 (1.10-1.77)</td>
<td>32</td>
<td>44</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.34 (0.87-2.06)</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.08 (0.75-1.55)</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.61 (0.41-0.91)</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Death due to other causes than the events above</td>
<td>1.08 (0.88-1.32)</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>Global Index</td>
<td>1.01 (0.91-1.12)</td>
<td>190</td>
<td>192</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.47 (1.04-2.08)</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>0.62 (0.42-0.93)</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.70 (0.63-0.79)</td>
<td>195</td>
<td>139</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE + MPA vs Placebo at 5.2 Years (95% CI*)</th>
<th>Placebo n = 8102</th>
<th>CE + MPA n = 8506</th>
<th>Absolute Risk per 10,000 Women-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.32 (1.02-1.72)</td>
<td>23</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>CHD death</td>
<td>1.18 (0.70-1.97)</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.26 (1.00-1.59)</td>
<td>30</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41 (1.07-1.85)</td>
<td>21</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.13 (1.39-3.25)</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63 (0.43-0.92)</td>
<td>16</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.83 (0.47-1.47)</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66 (0.45-0.98)</td>
<td>15</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Death due to causes other than the events above</td>
<td>0.92 (0.74-1.14)</td>
<td>40</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Global Index</td>
<td>1.15 (1.03-1.28)</td>
<td>151</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2.07 (1.49-2.87)</td>
<td>13</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>0.66 (0.44-0.98)</td>
<td>15</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Other osteoporotic fractures</td>
<td>0.77 (0.69-0.86)</td>
<td>170</td>
<td>131</td>
<td></td>
</tr>
</tbody>
</table>

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**

**Menopausal symptoms**

Short-term treatment of signs and symptoms of oestrogen deficiency due to the menopause, whether natural or surgically induced. In women with intact uteri, 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).

**Prevention of post-menopausal bone mineral density loss:**

Estraderm MX 50, 75 and 100 may be used for prevention of postmenopausal bone mineral density loss in women with an increased risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss. When prescribed solely for the prevention of postmenopausal bone mineral density loss, therapy should only be prescribed for women who are at high risk of future fracture and who are intolerant of, or contraindicated for, non-oestrogen products approved for prevention of bone mineral density loss. Lifestyle modifications and the risk-
benefit profile of Estraderm MX should be taken into careful consideration and discussed with
the patient to allow the patient to make an informed decision prior to prescribing (See
PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Estraderm MX 25 is not indicated for the prevention of post-menopausal bone mineral density
loss.

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 of the breast
- Known or suspected carcinoma of the endometrium or other oestrogen dependent neoplasia
- Endometriosis
- Vaginal bleeding of unknown origin
- Severe liver damage; i.e. cirrhosis, hepatitis or liver tumours
- 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
- Lactation
- Non-hysterectomised women unless on concomitant progestogen therapy
- Known hypersensitivity to the components of the transdermal system.

PRECAUTIONS

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

When initiating oestrogen/progestogen therapy for the prevention of postmenopausal bone
mineral density loss in women, 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 of continuing treatment is recommended.

1. Cardiovascular disorders

Oestrogen/progestogen therapy should not be used for the prevention of cardiovascular
disease.

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/m²) 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 Estraderm MX 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 or spotting, and treatment should be re-evaluated. 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. **Gallbladder disease**
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported.

5. **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.

6. **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.

7. **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.

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

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. These patients should be monitored closely.

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**
The oestrogen plus progestogen substudy of WHI reported that, after an average follow-up of 5.6 years, the relative risk of ovarian cancer for oestrogen plus progestogen versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for oestrogen plus progestogen versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of opposed and unopposed oestrogens in hysterectomised and non-hysterectomised women, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

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

j. **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.

k. **Exacerbation of other conditions**
Oestrogen therapy may cause an exacerbation of asthma, diabetes mellitus, 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): leiomyomas (uterine fibroids) or endometriosis, renal or hepatic disorders (e.g. liver adenoma), thromboembolic disorders, heart failure, hypertension, diabetes mellitus with or without vascular involvement, migraine or severe headache, systemic lupus erythematus, past endometriosis, endometrial hyperplasia, epilepsy, asthma, 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.

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

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.
1. **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.

2. **Severe anaphylactic/anaphylactoid reactions and angioedema**
Cases of anaphylactic/anaphylactoid reactions, which developed anytime during the course of Estraderm treatment and required emergency medical management, have been reported in the post marketing setting. Involvement of skin (hives, pruritis, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) has been noted. Angioedema involving the eye/eyelid, face, larynx, pharynx, tongue and extremity (hands, legs, ankles and fingers) with or without urticaria requiring medical intervention has occurred in the post marketing experience of using Estraderm. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop angioedema after treatment with Estraderm should not receive Estraderm again.

3. **Patient monitoring**
Estraderm MX, 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.

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 hormone replacement therapy and the need for hormone replacement therapy should be re-evaluated periodically.

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 or spotting, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out abnormality and the treatment should be re-evaluated.

Although observations to date suggest that oestrogens, including transdermal oestradiol taken in combination with low doses of transdermal progestogen, do not impair carbohydrate metabolism, diabetic women should be monitored during initiation of therapy until further information is available.
Women should be advised that Estraderm MX is not a contraceptive, nor will it restore fertility.

**Use in pregnancy (Category B1)**

Oestrogens must not be used during pregnancy (Refer to CONTRAINDICATIONS). Oestrogens may cause foetal harm when administered to pregnant woman.

**Use in breast feeding**

Estraderm MX must not be used while breast feeding.

**Paediatric use:**

Estraderm MX is not to be used in children.

**Use in the elderly:**

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.)

**Interaction with other medicines**

Preparations which induce microsomal liver enzymes, e.g. barbiturates, anticonvulsants (including hydantoins and carbamazepine), meprobamate, phenylbutazone, antibiotics (including rifampicin, rifabutin, nevirapine, efavirenz) may impair the activity of oestrogens and progestogens (irregular bleeding and recurrence of symptoms may occur). The extent of interference with transdermally administered oestradiol is not known.
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.

**Effect on laboratory tests**
Some laboratory tests may be influenced by oestrogen therapy, such as tests for glucose tolerance or thyroid function.

**ADVERSE EFFECTS**

Adverse drug reactions from clinical trials (Table 1) 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 1

<table>
<thead>
<tr>
<th>Neoplasms benign, malignant and unspecified (including cysts and polyps)</th>
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<tbody>
<tr>
<td>Uncommon:</td>
<td>Breast cancer.</td>
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<table>
<thead>
<tr>
<th>Immune system disorders</th>
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<tbody>
<tr>
<td>Very rare:</td>
<td>Anaphylactoid reaction (5).</td>
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<tr>
<td>Not known*:</td>
<td>Hypersensitivity (incl. anaphylactic reaction and angioedema)</td>
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<tr>
<th>Psychiatric disorders</th>
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<tbody>
<tr>
<td>Not known*:</td>
<td>Depression, nervousness, affect lability, libido disorder</td>
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<table>
<thead>
<tr>
<th>Nervous system disorders</th>
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<tbody>
<tr>
<td>Common:</td>
<td>Headache.</td>
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<tr>
<td>Rare:</td>
<td>Dizziness.</td>
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<tr>
<td>Not known*:</td>
<td>Migraine</td>
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<tr>
<th>Cardiac disorders</th>
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<tbody>
<tr>
<td>Very rare:</td>
<td>Embolism, hypertension, varicose veins (including exacerbation).</td>
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<tr>
<th>Gastrointestinal disorders</th>
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<tbody>
<tr>
<td>Common:</td>
<td>Nausea, abdominal pain, abdominal distension.</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Liver function tests abnormal, jaundice cholestatic</td>
</tr>
<tr>
<td>Not known*:</td>
<td>Cholelithiasis, vomiting, diarrhoea, gallbladder disorder</td>
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<tr>
<th>Skin and subcutaneous tissue disorders</th>
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<tbody>
<tr>
<td>Very rare:</td>
<td>Contact dermatitis, pigmentation disorders, generalised pruritus, generalised exanthema.</td>
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<tr>
<td>Not known*:</td>
<td>Alopecia, chloasma</td>
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<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tbody>
<tr>
<td>Rare:</td>
<td>Pain in extremity (leg pain (4))</td>
</tr>
<tr>
<td>Not known*:</td>
<td>Back pain</td>
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</tbody>
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<tr>
<th>Reproductive system and breast disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Very common:</td>
<td>Breast discomfort (1), breakthrough bleeding (2,3).</td>
</tr>
<tr>
<td>Not known*:</td>
<td>Endometrial hyperplasia, uterine leiomyoma, breast pain, breast tenderness</td>
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<tr>
<th>General disorders and administration site conditions</th>
<th></th>
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<tbody>
<tr>
<td>Very common:</td>
<td>Application site reactions.</td>
</tr>
<tr>
<td>Rare:</td>
<td>Oedema, weight increased or decreased.</td>
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</table>

(*) Reported in post-marketing experience.

(1) Sign of oestrogen effect, sign of overdose.

(2) Usually a sign of oestrogen overdose.

(3) If the oestrogen is adequately combined with a progestogen, regular withdrawal bleeding occurs, as observed in the normal menstrual cycle. Like any oestrogen therapy, transdermal oestrogen treatment can induce endometrial hyperplasia unless oestrogen intake is supplemented by adequate doses of a progestogen.

(4) Not related to thromboembolic disease and usually transient, lasting 3-6 weeks. If symptoms persist, the oestrogen dose should be reduced.

(5) Some of the women had a previous history of allergy or allergic disorders.

Other adverse reactions have been reported in association with some oestrogen-progestogen treatments: oestrogen-dependent neoplasms, benign and malignant (e.g. endometrial cancer), stroke, myocardial infarction, dementia, dry eyes, tear film composition., venous thromboembolism, e.g. deep leg or pelvic venous thrombosis and pulmonary embolism.
DOSAGE AND ADMINISTRATION

Initiation of therapy
Based on relief of menopausal symptoms, doses of Estraderm and Premarin† (conjugated oestrogens) which have been shown to produce the same effect are:

- Estraderm 25:    Premarin 0.3 mg
- Estraderm 50:    Premarin 0.625 mg
- Estraderm 100:  Premarin 1.25 mg

Estraderm 50 has also been shown to be clinically equivalent to 20 micrograms/day ethinyl-oestradiol.

In women who are not currently taking oral oestrogens, treatment with Estraderm MX can be initiated at once. In women who are currently taking oral oestrogens, treatment with Estraderm MX can be initiated on reappearance of symptoms, following discontinuation of oral therapy (generally within 5 to 7 days).

For all therapeutic indications, 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 should only be continued for as long as the benefits outweigh the risks for the individual (see PRECAUTIONS).

Signs and symptoms of oestrogen deficiency due to the menopause:
Treatment is normally initiated with Estraderm MX 50. Thereafter the dosage should be adapted to the needs of the individual; breast discomfort, breakthrough bleeding, water retention or bloating (if persisting for more than 6 weeks) are generally signs that the dose is too high and needs to be lowered. If, however, the dose selected fails to eliminate the signs and symptoms of oestrogen deficiency, a higher dose should be given. For maintenance therapy the lowest effective dose should always be used (see PRECAUTIONS).

Prevention of postmenopausal bone mineral density loss:
The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacological therapy. Postmenopausal women require an adequate daily intake of elemental calcium. Therefore when not contraindicated, calcium supplementation may be helpful for women with sub-optimal dietary intake. Vitamin D supplementation may also be required to ensure adequate daily intake in postmenopausal women.

Estraderm MX 50, 75 and 100 prevent the accelerated loss of bone density due to oestrogen deficiency and may be used for prevention of postmenopausal bone mineral density loss (see INDICATIONS). Estraderm MX 25 is insufficient to prevent post-menopausal bone mineral density loss. The effect is seen only while oestrogen replacement therapy continues and discontinuation may re-establish the natural rate of bone loss. The optimal duration of use to prevent fractures has not yet been determined. In patients with established bone mineral...
density loss and evidence of fracture therapy should be initiated with Estraderm MX 100. For maintenance therapy the lowest effective dose should always be used (see PRECAUTIONS).

**Continuous treatment:**
Continuous therapy is usually recommended. Estraderm MX should be applied twice weekly, i.e. the system should be changed once every 3 or 4 days. Each pack contains information on Estraderm MX and how to use it.

**In women with intact uteri:**
A progestogen should be administered sequentially for the first 10 - 14 (preferably 12) days of each calendar month to avoid overstimulation of the endometrium (see CLINICAL TRIALS). The addition of sufficient progestogen to induce secretory transformation of the endometrium is strongly recommended. Consideration should be given to a minimum progestogen dose of medroxyprogesterone acetate 10 mg, for at least 10 days of the month as a means of achieving endometrial transformation.

**Cyclic treatment:**
If required, Estraderm MX can be applied in a cyclic manner. In such cases, the progestogen should be taken on the last 12 days of each 3-week period of oestradiol administration, so that the 4th week of each cycle remains without any treatment. In either case i.e. continuous or cyclic treatment, a withdrawal bleed usually occurs following the progestogen administration.

**In hysterectomised women:**
Estraderm MX can be applied continuously without the coadministration of a progestogen.

**Method of administration:**
Remove Estraderm MX from the sachet and peel off the protective release liner. Apply the system to an area of clean, dry, intact skin on the buttocks.

The area of skin should be free from oil and from signs of irritation. Apply the adhesive side of the patch to the chosen spot and press firmly in place for at least 10 seconds.

Water contact (bathing, swimming or showering) should not affect the patch, although very hot water or steam may loosen it. In the unlikely event that a patch should fall off it can be reapplied. If it fails to adhere, a new system may be applied. In either case, the original treatment schedule should be continued.

- Estraderm MX 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, Estraderm MX should be applied to skin sites which will be covered by clothes.
- The patch must not be cut or torn.
OVERDOSAGE

Intentional overdosage with Estraderm MX is not likely, due to the pharmaceutical form and method of administration. However, if necessary, it can be reversed by removal of the patch(es). Signs of overdosage may be one or more of the following: breast discomfort, breakthrough bleeding, fluid retention and bloating (see DOSAGE and ADMINISTRATION). Toxicity is unlikely following acute single exposure; ingestion may cause nausea and vomiting.

Safety note concerning children:
Estraderm MX should be kept out of the reach of children both before and after use. Used systems contain residual oestradiol.

PRESENTATION AND STORAGE CONDITIONS

Estraderm MX 25 containing 0.75 mg oestradiol with an 11 cm² release area, 8’s.
Estraderm MX 50 containing 1.5 mg oestradiol with a 22 cm² release area, 8’s.
Estraderm MX 75 containing 2.25 mg oestradiol with a 33 cm² release area, 8’s.
Estraderm MX 100 containing 3.0 mg oestradiol with a 44 cm² release area, 8’s.
Colour - transparent.
Imprint Codes: Estraderm MX 25: CG GRG
              Estraderm MX 50: CG GSG
              Estraderm MX 75: CG HKH
              Estraderm MX 100: CG GTG

† Premarin is a registered trademark of Ayerst Laboratories Division of Wyeth Pharmaceuticals Pty Ltd.

NAME AND ADDRESS OF THE SPONSOR

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DATE OF APPROVAL
TGA Approval Date: 11 September 2000
Date of most recent amendment: 27 May 2011