PRODUCT MONOGRAPH

OESCLIM®

Estradiol-17β transdermal system

25 mcg / 24 hrs
37.5 mcg / 24 hrs
50 mcg / 24 hrs
75 mcg / 24 hrs
100 mcg / 24 hrs

Estrogen

Searchlight Pharma Inc.
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Date of Preparation:
April 28, 2015

Control # 183407
PHARMACOLOGICAL CLASSIFICATION

Estrogen

**Serious Warnings and Precautions**

The Women’s Health Initiative (WHI) trial examined the health benefits and risks of combined *estrogen plus progestin* therapy (n=16,608) and *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.\(^3\)\(^,\)\(^3\)\(^0\)\(^,\)\(^3\)\(^1\)

The *estrogen plus progestin* arm of the WHI trial indicated an increased risk of *myocardial infarction* (MI), *stroke*, *invasive breast cancer*, *pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.\(^3\)\(^1\)

The *estrogen-alone* arm of the WHI trial indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.\(^3\)\(^0\)

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at the **lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for the **shortest period** possible for the approved indication.
ACTIONS AND CLINICAL PHARMACOLOGY

OESCLIM® delivers estradiol-17β, a physiologic hormone, transdermally into the systemic circulation. Consequently, the estradiol-17β does not undergo first-pass liver and intestinal metabolism and estradiol-17β serum levels are comparable to those seen in premenopausal women in the early follicular phase of the menstrual cycle. Estradiol-17β stimulates target tissues such as the uterus, breast and vagina.

OESCLIM® contains estradiol-17β in an adhesive transdermal therapeutic system designed for application to an area of intact skin. It is designed to release controlled amounts of estradiol-17β continuously through the skin at a rate sufficient to raise circulating estradiol to premenopausal blood levels. Thus, OESCLIM® provides a replacement for physiological estradiol.

Description: Oesclim transdermal system has the following composition:
OESCLIM® patches are made up of a self-adhesive polymer matrix, which contains the estradiol, backed onto a rectangular foam mounting with rounded corners. The adhesive surface is covered by a transparent silicone-treated protective film which must be removed before use. This system provides excellent local tolerability and adhesion.

The active component of the system is estradiol-17β. The drug matrix provides a source for continuous delivery of drug for at least 4 days. The composition of each of the systems per unit area is identical.

The mean dose of estradiol-17β absorbed per 24 hours is about 25 mcg for OESCLIM® 25, 50 mcg for OESCLIM® 50 and 100 mcg for OESCLIM® 100. Physiological serum concentrations of estradiol, proportional to the quantity administered, are reached four hours after application of the patch.

**Clinical Pharmacology of Estrogen**

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) through a negative feedback mechanism and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

**Pharmacokinetics of OESCLIM®**

The pharmacokinetics of transdermally administered estradiol using OESCLIM® have been evaluated in a total of 138 healthy postmenopausal women in nine clinical and biopharmaceutic studies.

**Absorption**

Approximately twenty-four hours after the application, the mean values of estradiol maximal concentrations (Cmax) are 25, 81 and 108 pg/mL respectively with OESCLIM® 25, 50 and 100,
and estimated Cmax values are 38 and 75 pg/mL for OESCLIM® 37.5 and 75 respectively. Serum levels then remain practically constant throughout the application period (3-4 days). Seventy-two hours (3 days) after application, estradiol serum levels are practically the same as the mean values measured throughout the application period, i.e. 18, 46 and 64 pg/mL, respectively for OESCLIM® 25, 50 and 100, and the estimated average serum estradiol concentrations over 72 hours are 31 and 52 pg/mL for OESCLIM® 37.5 and 75 respectively.

Repeated applications over three weeks do not lead to accumulation of estradiol.

**Distribution**

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG), and to lesser degree to albumin.

**Metabolism**

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Since transdermally absorbed estradiol is not subject to first-pass liver metabolism, the ratio of serum concentrations of estradiol to either of its major metabolites, estrone or estrone sulfate, is closer to those observed in premenopausal women than when administered by the oral route of administration.

Mean ratios for E2/E1 (estradiol/estrone) serum concentrations during OESCLIM® patch application are similar to those observed in women before menopause, approximately equal to one.

**Excretion**

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Estradiol serum concentrations return to baseline values within eight hours after patch removal.
PIVOTAL CLINICAL TRIALS

Three clinical trials have been performed in order to evaluate the efficacy and safety of OESCLIM® in menopausal patients.

The aim of these studies was to evaluate the local skin tolerability of OESCLIM® in short- and long-term studies and to document its efficacy in comparison with placebo and with a reference oestrogen replacement therapy patch, ESTRADERM TTS® 50.

- The first clinical study (study # 1) was a randomized, placebo-controlled, double-blind study evaluating the efficacy of OESCLIM® in highly symptomatic patients (≥5 vasomotor symptoms per day) treated for 12 to 13 weeks.
- The second clinical study (study # 2) was an open-label, uncontrolled study evaluating the long-term local skin, specific and general tolerability of OESCLIM® in different types of menopausal patients (natural or surgical menopause) and using different therapeutic schedules (24 or 28-day discontinuous treatment regimen or continuous treatment regimen). Planned duration of treatment in this trial was 12 months.
- The third clinical study (study # 3) was a randomized, controlled study comparing the local skin tolerability, specific and general tolerability and efficacy of OESCLIM® 50 and ESTRADERM TTS® 50 in symptomatic menopausal patients treated for 16 weeks.

The studies #1 and #3 are regarded as pivotal for the evaluation of efficacy; study #2 confirmed the maintenance of efficacy during a 1-year long-term treatment. The studies #2 and #3 are regarded as major for the evaluation of safety.

The following table summarizes the most critical design features of the three main clinical trials.
<table>
<thead>
<tr>
<th>Study identification</th>
<th>Design</th>
<th>Primary aim</th>
<th>Secondary aims</th>
<th>Population</th>
<th>Evaluated patients</th>
<th>Treatment features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study #1</td>
<td>Randomized</td>
<td>Efficacy on vasomotor symptoms at 12 weeks</td>
<td>Evaluate: - efficacy on other menopause related symptoms - local skin tolerability - specific tolerability to estrogen therapy - general safety - treatment acceptability.</td>
<td>Symptomatic naturally menopausal women with ≥ 5 hot flushes per day 4/7 days and ≥ 1 night sweat per 24 hours 4/7 nights during 7-day self-assessment</td>
<td>61</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>Double-blind</td>
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<td>No progestogen</td>
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<td></td>
<td>2 parallel groups</td>
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<td></td>
<td></td>
<td></td>
<td>Fixed dose: OESCLIM® 50 or placebo</td>
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<tr>
<td></td>
<td>Placebo-control</td>
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<td></td>
<td></td>
<td>2 systems per week</td>
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<td></td>
<td>Multicentre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 to 13 weeks of treatment</td>
</tr>
<tr>
<td>Study #2</td>
<td>Uncontrolled</td>
<td>Local skin tolerability over one year</td>
<td>Evaluate specific tolerability to Hormone Replacement Therapy; general safety and efficacy.</td>
<td>Female patients showing signs of estrogen deficiency related to the menopause or patients treated with other hormone replacement therapy for menopausal symptoms and having undergone a one-month wash-out period</td>
<td>222</td>
<td>24 or 28-day discontinuous or continuous</td>
</tr>
<tr>
<td></td>
<td>Open-label</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fixed dose for 3 months: OESCLIM® 50, flexible after 3 months: OESCLIM® 25, 50 or 100</td>
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<tr>
<td></td>
<td>Multicentre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total of 12 months of treatment with concomitant progestogen treatment given in sequential fashion during the last 12 to 16 days of cycles</td>
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</tr>
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<td>Study identification</td>
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<td>Secondary aims</td>
<td>Population</td>
<td>Evaluated patients</td>
<td>Treatment features</td>
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</tr>
<tr>
<td>Study #3</td>
<td>Randomized</td>
<td>Local skin tolerability after 16 weeks of treatment.</td>
<td>Compare OESCLIM® 50 and Estraderm TTS® 50 in terms of efficacy, general tolerability, specific tolerability to estrogen treatment.</td>
<td>Symptomatic menopausal patients with ≥ 1 hot flush and ≥ 1 night sweat during the 7-day self-assessment</td>
<td>281 OESCLIM® 50: 143 Estraderm TTS® 50: 138</td>
<td>24-day discontinuous Treatment with OESCLIM® 50 or Estraderm TTS® 50 during 4 cycles of 28 days per cycle (16 weeks) with concomitant progestogen treatment given in sequential fashion during the last 12 days of estrogen therapy</td>
</tr>
</tbody>
</table>

**Discussion of Clinical Results**

The efficacy of OESCLIM® 50 in alleviating subjective vasomotor symptoms was documented in the 2 controlled studies, the placebo-controlled study (study # 1) and the study comparing OESCLIM® 50 and ESTRADERM TTS® 50 (study # 3). Supportive efficacy data over 1 year of treatment were also obtained in the long-term, uncontrolled study (study # 2). Study results showed that in highly symptomatic patients (≥ 5 vasomotor symptoms per day, i.e. hot flushes and night sweats), OESCLIM® 50 provided a near maximum effect (i.e. maximum decrease in the number of vasomotor symptoms, from the inclusion visit (Vi) to the end of study visit (Vf)) after 4 weeks (V1) of treatment with mean percent decreases from baseline values (i.e. hot flushes and night sweats measured before treatment) of 71% to 89%, and percentages of patients with complete relief (i.e. no vasomotor symptoms reported) of 30% to 43%, in Studies 3 and 1 respectively. In Study 2, OESCLIM® 50 provided the maximum effect after 2 months (V1) of treatment with a mean percent decrease from baseline value of 91%, and percentage of patients with complete relief of 75%. After 12 to 16 weeks of treatment, in the same populations, OESCLIM® 50 provided mean percent decreases from baseline values of 92% to 97%, and percentages of patients with complete relief of 72% to 86%, depending on the study (see tables below for detailed study results).
Mean number of vasomotor symptoms (hot flushes and night sweats) per day at each visit in all patients who were evaluated for efficacy.

<table>
<thead>
<tr>
<th>Study # 1</th>
<th>Inclusion Visit</th>
<th>Study Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (Vi)</td>
<td>After 4 weeks (V1)</td>
</tr>
<tr>
<td>Mean + SD</td>
<td>9.31 ± 4.24</td>
<td>1.15 ± 2.14 (89.2%)</td>
</tr>
</tbody>
</table>

Study # 3

<table>
<thead>
<tr>
<th>Study # 3</th>
<th>Inclusion Visit</th>
<th>Study Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (Vi)</td>
<td>After 4 weeks (V1)</td>
</tr>
<tr>
<td>Mean + SD</td>
<td>9.95 ± 6.29</td>
<td>2.54 ± 2.94 (71.0%)</td>
</tr>
</tbody>
</table>

Mean number of vasomotor symptoms (hot flushes and night sweats) per day at each visit in all patients who were evaluated for efficacy.

<table>
<thead>
<tr>
<th>Study # 2</th>
<th>Inclusion Visit</th>
<th>Study Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (Vi)</td>
<td>After 2 months (V1)</td>
</tr>
<tr>
<td>Mean + SD</td>
<td>5.35 ± 4.80</td>
<td>0.47 ± 1.32 (91.2%)</td>
</tr>
</tbody>
</table>

Number of patients obtaining complete relief from vasomotor symptoms (hot flushes and night sweats) at each visit of all patients evaluated for efficacy.

<table>
<thead>
<tr>
<th>Study # 1</th>
<th>Oesclim 50 (n=28)</th>
<th>After 4 weeks (V1)</th>
<th>After 8 weeks (V2)</th>
<th>After 12 weeks (Vf)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 (42.9%)</td>
<td>20 (71.4%)</td>
<td>24 (85.7%)</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study # 3</th>
<th>Oesclim 50 (n=50)</th>
<th>After 4 weeks (V1)</th>
<th>After 8 weeks (V2)</th>
<th>After 12 weeks (V3)</th>
<th>After 16 weeks (Vf)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 (30.0%)</td>
<td>29 (58.0%)</td>
<td>33 (66.0%)</td>
<td>36 (72.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients obtaining complete relief from vasomotor symptoms (hot flushes and night sweats) at each visit of all patients evaluated for efficacy.

<table>
<thead>
<tr>
<th>Study # 2</th>
<th>Oesclim 50 (n=142)</th>
<th>After 2 months (V1)</th>
<th>After 6 months (V2)</th>
<th>After 11 months (V3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>102 (75.0%)</td>
<td>79 (79.0%)</td>
<td>63 (75.9%)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion of tolerability

Three aspects of tolerability were studied:

- local skin tolerability;
- drug specific tolerability, including the signs described by the investigators as due to hyperestrogenism or directly due to treatment with HRT;
- general tolerability, covering all other adverse events.

Results on local skin tolerability

The number of OESCLIM®-treated patients presenting at least one local skin reaction were 9, 85, and 37 in Studies #1, #2, and #3 respectively. The percentages were lowest in the studies of short duration (28.13% after 12 weeks for study #1 and 25.9% after 16 weeks for study #3), and higher in the 1-year treatment study #2 (38.32%).

In all three trials, approximately 4.2% of all applications caused a local skin reaction (i.e. number of application site reaction/total number of applications), irrespective of the duration of exposure.

For all 3 trials, the most frequent types of application site reactions with OESCLIM® were erythema, 2.7%, and pruritus, 3.0%.

Of the 397 OESCLIM®-treated patients (32 in Study #1; 222 in Study #2; 143 in Study #3) evaluated for local skin tolerability across the clinical trials, 7 (1.8%) patients withdrew due to application site reactions from the trials; 0 patients in Study #1, 6 patients (2.7%) in Study #2 and 1 patient (0.7%) in Study #3.

Results on specific hormone replacement therapy tolerability

Symptoms of specific estrogen therapy intolerance were reported by 197 patients treated with OESCLIM® among 397 patients in the 3 clinical studies: 17 (53.1%) in Study #1, 138 (62.2%) in Study #2, and 52 (36.4%) in Study #3. 119 OESCLIM®-treated patients presented signs of hyperestrogenism: 14 (43.7%) in Study #1, 76 (34.2%) in Study #2, and 26 (18.2%) in Study #3. 116 non-hysterectomized patients presented metrorrhagia or spotting: 8 (25.0%) in Study #1, 76 (36.9%) in Study #2, and 29 (20.3%) in Study #3.

The most frequent sign of hyperestrogenism was mastodynia (breast pain): 7 (21.9%) in Study #1, 66 (29.5%) in Study #2 and 18 (12.6%) in Study #3.

During the course of the 3 clinical trials, 23 patients (5.8%) treated with active OESCLIM® withdrew due to signs of hyperestrogenism and/or metrorrhagia: 1 patient (3.1%) in Study #1, 17 patients (7.7%) in Study #2 and 5 patients (3.5%) in Study #3. Four (1.0%) of these patients withdrew for metrorrhagia alone: 1 in Study #1, 3 in Study #2 and 0 in Study #3. Nine (2.3%) patients withdrew for adverse events related to the treatment that were not considered signs of hyperestrogenism: 0 in Study #1, 8 in Study #2 and 1 in Study #3.
Results on general tolerability

General tolerability includes all adverse events described by the investigators which were neither signs of hyperestrogenism, nor metrorrhagia, nor symptoms attributed to the study treatment, nor application site reactions.

A total of 150 patients presented at least one adverse event not related to OESCLIM® during the course of the 3 studies: 7 patients (21.9%) in Study #1, 106 patients (47.3%) in Study #2 and 37 patients (25.9%) in Study #3. In general, these events resolved spontaneously. Forty two (10.6%) patients withdrew from the trials due to general adverse events: 1 patient in Study #1, 34 patients in Study #2 and 7 patients in Study #3.

INDICATIONS AND CLINICAL USE

OESCLIM® is indicated for the relief of menopausal and post menopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

OESCLIM® should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

CONTRAINDICATIONS

Estrogen and estrogen/progestin combinations are contraindicated in patients with any of the following conditions/disorders:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Pharmaceutical Information section of the product monograph.
- Active hepatic dysfunction or disease, especially of the obstructive type.
- Personal history of known or suspected estrogen-dependent malignant neoplasia (e.g. breast or endometrium).
- Endometrial hyperplasia.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy.
- Lactation.
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Classical migraine.
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis.
- Partial or complete loss of vision due to ophthalmic vascular disease.
- Porphyria.
WARNINGS

See Boxed Warnings at the front page.

CARDIOVASCULAR DISORDERS

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of estrogen plus progestin is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women. The results of the WHI trial indicate that the use of estrogen-alone and estrogen plus progestin is associated with an increased risk of stroke in postmenopausal women.

WHI trial findings

In the combined estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo).
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).

In the estrogen-alone arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were:

- 12 more cases of stroke (44 on estrogen-alone therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.

HERS and HERS II findings

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus 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 hormone-treated group than in the placebo group in year 1, but not during the subsequent years.
From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.\textsuperscript{6}

In clinical trials carried out with OESCLIM\textsuperscript{®}, there were no reported cases of stroke or coronary heart disease.

**BREAST CANCER**

Available epidemiological data indicate that the use of combined estrogen plus progestin by postmenopausal women is associated with an increased risk of invasive breast cancer. In the estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).\textsuperscript{31}

The WHI study also reported that the invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs. 1.5 cm [0.9], respectively; \( P=0.04 \)) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the estrogen plus progestin group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.\textsuperscript{3}

In the estrogen-alone arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.\textsuperscript{30}

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease. There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy). Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.
The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

*Instructions for regular self-examination of the breasts should be included in this counselling.*

**VENOUS THROMBOEMBOLISM**

Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the estrogen plus progestin arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.31

In the estrogen-alone arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.30

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition) and severe obesity (body mass index > 30 kg/m²). The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens should be discontinued at least 4 weeks before major surgery, which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.
ENDOMETRIAL HYPERPLASIA & ENDOMETRIAL CARCINOMA

Estrogen-only HRT increases the risk of endometrial hyperplasia (if taken by women with intact uteri).

The incidence of endometrial hyperplasia is lowered with sequential co-administration of a progestin (see administration of progestins under DOSAGE AND ADMINISTRATION). One case of endometrial hyperplasia (0.45%) among 222 patients in the OESCLIM® 50-treated group was reported in an uncontrolled clinical trial conducted to evaluate the tolerability of OESCLIM® over a twelve-month period. Time of onset was between 271-360 days into the treatment phase in a patient treated continuously with OESCLIM® 50. The patient was withdrawn 343 days after the inclusion visit (Vi), after 329 days of exposure to the transdermal systems.

Estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

GALLBLADDER DISEASE

A 2- to 4-fold increase in gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

DERMATOLOGIC HYPERSENSITIVITY

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

BENIGN HEPATIC ADENOMAS

Benign hepatic adenomas have been associated with the use of combined estrogen and progestagen oral contraceptives. Although benign and rare, these tumours may rupture and cause death from intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestagen preparations, but they should be considered if abdominal pain and tenderness, abdominal mass, or hypovolemic shock occurs in patients receiving estrogen.

Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The causal relationship of this malignancy to these drugs is not known.
DEMENTIA

Available epidemiological data indicate that the use of combined estrogen plus progestin in women age 65 and over may increase the risk of developing probable dementia.

The Women’s Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (estrogen plus progestin or estrogen-alone) reduces the risk of dementia in women aged 65 and over and free of dementia at baseline.26,27

In the estrogen plus progestin arm of the WHIMS (n=4532), women with an intact uterus were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).27

In the estrogen-alone arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on estrogen-alone versus 25 on placebo), although this difference did not reach statistical significance.26

When data from the estrogen plus progestin arm of the WHIMS and the estrogen-alone arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on estrogen plus progestin or estrogen-alone versus 23 on placebo).26
PRECAUTIONS

- Before OESCLIM® is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. An endometrial biopsy should be done when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

- The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician. It is important that patients are encouraged to practice frequent self-examination of the breasts.

- Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt diagnostic measures like hysteroscopy, endometrial biopsy or curettage to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

- Pre-existing uterine leiomyoma may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyoma requires discontinuation of medication and appropriate investigation.

- Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

- Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

- Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.

- If feasible, estrogens should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

- Women using hormonal replacement therapy (HRT) sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood
pressure in previously normotensive or hypertensive patients should be investigated and HRT therapy may have to be discontinued.

- Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. Treatment should be stopped if there is an increase in epileptic seizures. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

- Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

- A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

- Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

- Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under Laboratory Tests.

### Drug Interactions

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes, (e.g., barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens. The extent of interference with transdermally administered estradiol-17β is not known. Given that the first-pass effect in the liver is avoided by transdermal administration, transdermally applied estrogens may be less affected by enzyme inducers than oral estrogen preparations.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.
It was found that some herbal products (e.g. St. John’s wort), which are available as over-the-counter (OTC) products, may affect metabolism, and therefore, efficacy and safety of estrogen/progestin products.

Physicians and other healthcare providers should be aware of other non-prescription products concomitantly used by the patient, including herbal and natural products, widely available in health food stores.

**Laboratory Tests**

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T₄) as measured by column or radioimmunoassay; free T₃ resin uptake is decreased, reflecting the elevated TBG; free T₄ concentration is unaltered;
- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged.
- impaired glucose tolerance;
- reduced serum folate concentration;
- increased serum triglycerides and phospholipids concentration.

In clinical trials with transdermal estradiol-17β, no effect on fibrinogen, antithrombin III, TBG, CBG or SHBG and decreases in serum triglycerides were seen.²

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for 2 to 4 weeks. The pathologist should be informed that the patient is receiving estrogen therapy when relevant specimens are submitted.
ADVERSE REACTIONS

See Warnings and Precautions regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The most commonly reported adverse reaction to OESCLIM® in clinical trials was application site reaction. 9 patients (28.1 %) in Study #1, 85 patients (38.3 %) in Study #2 and 37 patients (25.9 %) in Study #3 presented at least one local skin reaction. In all three clinical trials, 4.2% of all applications caused local skin reactions, which included redness, itching, spots, burning and swelling. Of the 22,239 applications in the three clinical trials, 1,017 (4.6%) patches became detached. The second most frequent adverse reactions were symptoms of specific estrogen therapy intolerance reported by a total of 193 patients (48.6 %) treated with OESCLIM® in the 3 clinical trials: 119 (30%) presented signs of hyperestrogenism including mastodynia (38.8 % to 53.8 % of the cases of hyperestrogenism), 116 (38.5 %) non-hysterectomised patients presented metrorrhagia and spotting.

The following adverse reactions have been reported with the use of estrogen/progestin combination in general.

Gastrointestinal
Nausea; vomiting; abdominal discomfort (cramps, pain, pressure); bloating; gallbladder disorder, asymptomatic impaired liver function; cholestatic jaundice.

Genitourinary
Breakthrough bleeding, spotting; change in menstrual flow, dysmenorrhea; vaginal itching/discharge, dyspareunia, dysuria, endometrial hyperplasia, pre-menstrual-like syndrome; reactivation of endometriosis; cystitis; changes in cervical erosion and amount of cervical secretion.

Skin
Cloasma or melasma, which may persist when drug is discontinued; allergic contact dermatitis; reversible post-inflammatory pigmentation; general pruritus and exanthema; pigmentation of the skin; erythema nodosum; erythema multiforme; hemorrhagic skin eruptions; loss of scalp hair; hirsutism; acne; isolated cases of anaphylactoid reactions (some of the patients had a history of previous allergy or allergic disorders).

Endocrine
Breast swelling and tenderness; increased blood sugar levels; decreased glucose tolerance; sodium retention.
Cardiovascular/Hematologic
Palpitations; isolated cases of: thrombophlebitis, thromboembolic disorders; increase in blood pressure (see Warnings and Precautions). Coronary thrombosis; altered coagulation tests (see Precautions, Laboratory Tests).

Central Nervous System
Aggravation of migraine episodes; headaches; mental depression; nervousness; dizziness; fatigue; irritability; neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis).

Ophthalmic
Visual disturbances; steepening of the corneal curvature; intolerance to contact lenses; neuro-ocular lesions (see Central Nervous System above).

Miscellaneous
Changes in appetite; changes in body weight; edema; neuritis; change in libido; musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

If adverse symptoms persist, the prescription of HRT should be reconsidered.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Treatment

Owing to the mode of administration (transdermal), plasma levels of estradiol-17β can be rapidly reduced by removal of the patch. Symptomatic treatment should be given.
DOSAGE AND ADMINISTRATION

Dosage

Apply OESCLIM® twice a week, i.e. apply one patch for a three day application period and the next for a four day application period.

The treatment is generally initiated with OESCLIM® 25, 37.5 or 50. The initial selection of the dose of estradiol can be based on the type and severity of the patient’s symptomatology. Depending on the clinical response to treatment, the dosage must then be adjusted to the individual’s needs. If the chosen dose does not correct the symptoms of estrogen deficiency, the dose may be increased. Breast tenderness and/or metrorrhagia in general indicates that the dose is too high and needs to be lowered.

Two therapeutic schedules can be used with OESCLIM®:

* discontinuous (cyclic): 24–28 days treatment followed by a two to seven day treatment-free period;

* continuous (noncyclic): no treatment-free period.

Continuous, noncyclic therapy may be indicated in hysterectomized women or in cases where the signs and symptoms of estrogen deficiency become problematic during the treatment-free interval.

In women with an intact uterus, sequential treatment with sufficient progestogen to inhibit endometrial hyperplasia and to induce secretory transformation of the endometrium is mandatory. The progestogen may be administered according to one of the two following regimens:

- If OESCLIM® is administered on a discontinuous schedule, the progestogen should be administered for at least the last 12 days of the estradiol treatment; thus there is no hormone administration during the treatment-free period of each cycle.

- If OESCLIM® is administered on a continuous schedule, the progestogen is recommended for at least 12 sequential days per month.

In both cases breakthrough bleeding may occur after the progestogen is stopped. Unexpected or abnormal bleeding in such patients is an indication for prompt diagnostic measures.
The lowest clinically effective dose of each hormone should be used.

Administration

Remove the OESCLIM® transdermal system from its pouch only just before using. Once the protective liner has been removed, OESCLIM® must be applied immediately onto the buttock, the torso (iliac fossa, abdomen) or the upper part of the arm or thigh at a site free of major folds and away from areas where the system can be rubbed off by tight clothing.

The skin must be dry and free from any irritation and not treated with oily or greasy products.

**Do not apply OESCLIM® to the abdomen,** if a dose of OESCLIM® has been previously adjusted with the patch applied to other sites of the body, as this might change the amount of hormone delivered.

**OESCLIM® must not be applied to the breasts. When a patch is removed, the next patch should not be applied to the same site.**

It is possible to shower or take a bath while wearing an OESCLIM® transdermal system. In the exceptional circumstance that a transdermal system should fall off (hyperperspiration, abnormal rubbing by clothing), it is recommended that the same system be reapplied on dry skin. If this is not possible, use a new transdermal patch which will be removed on the anticipated date. Thereafter the cycle of changing of the patch will continue according to the original schedule.
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Estradiol hemihydrate (INN)

Chemical name: \((17\beta)-\text{Estra-1,3,5(10)-triene-3,17-diol hemihydrate}\)

Structural formula:

\[
\begin{align*}
\text{HO} \\
\text{CH}_3 \\
\text{OH}
\end{align*}
\]

Molecular formula: \(C_{18}H_{24}O_2, \frac{1}{2}H_2O\)

Molecular weight: 281.4

Description: White or almost white crystalline powder or colourless crystals

Melting point: 175°C to 180°C

Solubility: Practically insoluble in water, soluble in acetone, sparingly soluble in alcohol, slightly soluble in ether and in methylene chloride
Drug Product

Description: Rectangular transdermal system (11, 16.5, 22, 33 or 44 cm²), with rounded corners, consisting of a transparent adhesive layer laminated onto a beige foam backing. The adhesive is protected by a transparent peelable release liner.

Composition: Ethylene/vinyl acetate copolymer, dipropylene glycol, octyl dodecanol, ethylcellulose.

Stability and Storage Recommendations

Store at room temperature (15–25°C). Avoid freezing. Do not store unpouched. Apply immediately upon removal from the protective pouch. Keep out of the reach of children both before and after use. After removal of the patch fold it in half, with the adhesive side inwards, before discarding.

AVAILABILITY OF DOSAGE FORMS

OESCLIM® 25: Each rectangular (11 cm²) transdermal system contains estradiol hemihydrate corresponding to 5 mg estradiol for delivery of estradiol 25 mcg/24 hrs. Patient pack of 8 systems.

OESCLIM® 37.5: Each rectangular (16.5 cm²) transdermal system contains estradiol hemihydrate corresponding to 7.5 mg estradiol for delivery of estradiol 37.5 mcg/24 hrs. Patient pack of 8 systems.

OESCLIM® 50: Each rectangular (22 cm²) transdermal system contains estradiol hemihydrate corresponding to 10 mg estradiol for delivery of estradiol 50 mcg/24 hrs. Patient pack of 8 systems.

OESCLIM® 75: Each rectangular (33 cm²) transdermal system contains estradiol hemihydrate corresponding to 15 mg estradiol for delivery of estradiol 75 mcg/24 hrs. Patient pack of 8 systems.

OESCLIM® 100: Each rectangular (44 cm²) transdermal system contains estradiol hemihydrate corresponding to 20 mg estradiol for delivery of estradiol 100 mcg/24 hrs. Patient pack of 8 systems.
PHARMACOLOGY

Estrogens (naturally occurring, their derivatives or synthetic estrogens) are the basis of postmenopausal Hormonal Replacement Therapy (HRT). Mashchak et al. \(^{16}\) compared the metabolic effects of different estrogens given orally and reported that the physiological hormone estradiol induced the least metabolic disturbances.

It has been clearly demonstrated that estradiol is metabolised to a lesser extent when administered by the transdermal route than by the oral route. The transdermal route, by avoiding “first-pass” metabolism, allows a considerable reduction in the quantity of estradiol administered. Treatment with a patch that delivers 100 \(\mu\)g of estradiol per day results in mean serum levels of estradiol comparable to those obtained with 2 mg/day of micronised estradiol given orally. Moreover, oral estradiol administration results in serum concentrations of estrone, estrone glucuronide and estrone sulphate that are 3, 13 and 4 fold higher respectively, than after transdermal administration. Thus, after transdermal estradiol administration, the estradiol/estrone ratio in the serum is close to 1, the normal value present before menopause (this ratio is approximately 0.2 when estradiol is administered orally). \(^{21}\)

Similarly, serum levels of estradiol glucuronides and sulphates, as well as oestriol glucuronides and sulphates, are 11, 5, 7 and 10 fold higher, respectively, after oral treatment than after transdermal treatment. \(^{25}\)

The transdermal administration of estradiol provides dose levels of estradiol and estradiol metabolites that more closely approach the physiological than the oral route.

The significant difference in estradiol metabolism between the oral and transdermal routes is also evident in the results of urinary elimination. The concentration of estradiol and estrone conjugates in the urine is in fact 56 \(\mu\)g/g and 183 \(\mu\)g/g of creatinine, respectively, after 3 days of treatment with 2 mg/day of oral estradiol. After a 3-day application of a patch which delivers 100 \(\mu\)g/day, the urinary conjugates of estradiol and estrone did not exceed 4.2 \(\mu\)g/g and 11.3 \(\mu\)g/g of creatinine, respectively. \(^{4}\)

A similar situation exists for estradiol distribution studies. Estrogens in the blood stream are bound to albumin, sex hormone-binding globulin (SHBG), cortisol-binding globulin and alpha-1 glycoproteins. It has been shown that three months treatment with 0.1 mg/day of estradiol by the transdermal route does not significantly modify estradiol or estrone binding to plasma transport proteins. \(^{10}\)

Moreover, the transdermal route avoids unwanted metabolic effects following oral administration, such as an increase in angiotensinogen or a decrease in antithrombin III. \(^{10,11}\)
TOXICOLOGY

Excess estradiol is one of the pre-disposing factors in the development of certain tumours, principally in the uterus, mammary and pituitary glands. These effects have been studied after long-term administration in rodents. Exposure in dogs and in primates has not been sufficiently long to reveal this type of activity. However, hyperplasia of the endometrium and the mammary glands, and increased secretory activity of the pituitary suggest that effects occurred at these sites in the above species.

In hamsters, tumour-inducing effects of mesenchymatous origin were observed in the kidneys. No such effects occur in rats, mice or humans. Hepatocarcinomas have been reported in rats after 9 and 12 months treatment with synthetic estrogens such as ethynyl estradiol and mestranol. Such effects have not been reported for estradiol-17β. Furthermore, estradiol administered by the transdermal route does not undergo “first pass” effect through the liver and thus avoids deleterious metabolic effects.

Estradiol is devoid of any mutagenic and/or clastogenic potential. Aneuploidy effects have been observed in vitro.

The carcinogenic potential (uterus, mammary glands and pituitary) of estradiol has been clearly established in animals. Its pre-neoplastic effects on the endometrium are reduced if a progestogen is associated with the estradiol.

No relationship has been established between the risk of pituitary tumours and estrogen treatment in postmenopausal women. Estradiol is contra-indicated in women presenting with tumours of the breast or the pituitary.

The OESCLIM® transdermal system was tested in the rabbit and the guinea-pig to evaluate its irritative and sensitizing potential. Three duplicate studies, two acute and two sub-acute local tolerability studies in rabbits and two sensitization studies in guinea-pigs, were performed. The patch was found to be only slightly irritating and had no sensitizing potential.
Please read this PATIENT INFORMATION carefully before you start using OESCLIM® (estradiol transdermal system) and each time you have your prescription refilled. This leaflet includes information on estrogens and progestins, how to use OESCLIM®, and precautions to take when using OESCLIM®. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment. If you have any questions or concerns you should speak with your doctor or pharmacist.

**Serious Warnings and Precautions**

The Women’s Health Initiative (WHI) trial assessed the health benefits and risks of oral combined *estrogen plus progestin* therapy and *estrogen-alone* therapy in postmenopausal women.

The *estrogen plus progestin* arm of the WHI trial indicated increased risk of myocardial infarction (heart attack), stroke, invasive breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women receiving treatment with conjugated equine estrogens (an estrogen medication) and medroxyprogesterone acetate (a progestin medication).

The *estrogen-alone* arm of the WHI trial indicated increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) receiving treatment with conjugated equine estrogens.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at the lowest effective dose and for the shortest period of time possible. Regular medical follow-up is advised.
INTRODUCTION: What is OESCLIM®?

OESCLIM®
25, 37.5, 50, 75 or 100 micrograms/24 hours
Transdermal System (patch)

OESCLIM® is a transdermal system which contains estradiol, a natural estrogen.
Your doctor has prescribed OESCLIM® for you after a careful review of your medical needs.
Use it only as directed and do not give it to anyone else. OESCLIM® should be used only under
the supervision of a doctor, with regular follow-up at least once a year to identify side effects
associated with its use. Your first follow-up visit should be within 3 to 6 months of starting
treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and a
pelvic exam. You should have a mammogram before starting treatment and at regular intervals
as recommended by your doctor, and check your breasts regularly for lumps. Your doctor may
recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with
your doctor. You should talk regularly with your doctor about whether you still need treatment
with HRT.

INDICATIONS: OESCLIM® is approved for use in the following situations:

OESCLIM® has been given to you to relieve symptoms due to the lack of estrogen that occurs
during or after menopause or because of surgery (see explanation below).

Estrogens

1. Estrogens are used to reduce moderate or severe menopausal symptoms. Your body
   normally makes estrogens and progestins (female hormones) mainly in the ovaries.
   Between the ages of 45-55, the ovaries gradually stop making estrogens. This leads to a
decrease in body estrogen levels and a natural menopause (the end of monthly menstrual
periods). If both ovaries are removed during an operation before natural menopause
takes place, the sudden decrease in estrogen levels causes "surgical menopause".

   Menopause is not a disease; it is a natural life event and different women experience
menopause and its symptoms differently. Not all women experience the obvious
symptoms of estrogen deficiency. When the estrogen levels begin decreasing, some
women develop very uncomfortable symptoms, such as feelings of warmth in the face,
neck and chest, or sudden intense episodes of heat and sweating ("hot flushes" or "hot
flashes"). Using estrogen drugs can help the body adjust to lower estrogen levels and
reduce these symptoms.

2. Estrogens are used to treat vulval and vaginal atrophy. Some women may also develop
   vulval or vaginal atrophy (itching, burning or dryness in or around the vagina, difficulty
or burning on urination) in association with menopause. These changes may be improved by estrogen therapy.

**Progestins**

Progestins used in hormone replacement therapy are similar to the female sex hormone progesterone. During the childbearing years, progesterone is responsible for the regulation of the menstrual cycle. The estradiol delivered by OESCLIM® not only relieves your menopausal symptoms, but like estrogens produced by your body, may also stimulate growth of the inner lining of the uterus, the endometrium. In menopausal and post-menopausal women with an intact uterus, stimulation of growth of the endometrium may result in irregular bleeding. In some cases this may progress into a disorder of the uterus known as endometrial hyperplasia (overgrowth of the lining of the uterus). Endometrial hyperplasia increases the risk of developing endometrial cancer (cancer of the lining of the uterus).

The development of estrogen-mediated disorders of the uterus can be reduced if a progestin is given regularly for a certain number of days with your estrogen replacement therapy. Each cycle of progestin administration should include a periodic bleeding, whereby the inner lining of the uterus is regularly shed, thus protecting against endometrial hyperplasia.

If your uterus has been surgically removed, endometrial hyperplasia cannot occur and cyclic administration of a progestin is not necessary.

**RESTRICTIONS ON USE: WHO SHOULDN’T TAKE OESCLIM®:**

Certain medical conditions may be aggravated by estrogens; therefore estrogens should not be used at all or should be used with precaution under these conditions.

**Estrogens should not be used during pregnancy.** Since pregnancy may be possible early in menopause while you are still having spontaneous periods, the use of non-hormonal birth control should be discussed with your physician at this time. If you take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.

**Estrogen should not be used if you are breast-feeding.**

Before using OESCLIM®, be sure to tell your doctor if you have ever had any of the following medical problems. OESCLIM® should not be used if you have any of the following conditions:

- allergic or unusual reaction to any of the ingredients of OESCLIM® (see section called Pharmaceutical Information)
- active liver disease
- a personal history of breast cancer or endometrial cancer (cancer of the lining of the uterus)
- undiagnosed or unusual vaginal bleeding
- known or suspected pregnancy
- stroke, heart attack, or coronary heart disease
- migraine headaches
- active or personal history of venous thromboembolism (blood clots in the large veins or lungs) or thrombophlebitis (inflammation of the veins)
- partial or complete loss of vision due to blood vessel disease of the eye
- porphyria (a disease of blood pigment)
- endometrial hyperplasia (overgrowth of the lining of the uterus)
WARNINGS AND PRECAUTIONS

Breast Cancer

In the estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period there were:

• 8 more cases of invasive breast cancer.

In the estrogen-alone arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period there was:

• no meaningful difference in the rate of invasive breast cancer.

Estrogens should not be taken by women who have a personal history of breast cancer. In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting hormone replacement therapy.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review technique for breast self-examination with your doctor.

Overgrowth of the lining of the uterus and cancer of the uterus

The use of estrogen-alone therapy by post menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus). If you still have your uterus you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not required as part of hormone replacement therapy in women who have had a hysterectomy.
Heart Disease and Stroke

In the estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period there were:

• 8 more cases of stroke
• 7 more cases of coronary heart disease.

In the estrogen-alone arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

• 12 more cases of stroke
• no meaningful difference in the rate of coronary heart disease.

Abnormal Blood Clotting

In the estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period there were:

• 18 more cases of blood clots in the lungs and large veins.

In the estrogen-alone arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were:

• 7 more cases of blood clots in the lungs and large veins

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

Gallbladder Disease

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.
Dementia

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial involving women aged 65 and older.
In the estrogen plus progestin arm of the WHIMS, among 10,000 women over a one-year period there were:

- 23 more cases of probable dementia (loss of memory and intellectual function).

In the estrogen-alone arm of the WHIMS involving women with prior hysterectomy, among 10,000 women over a one-year period there was:

- no meaningful difference in the rate of probable dementia.

Benign Liver Tumours

Benign liver tumours have been associated with the use of combined estrogen and progestagen oral contraceptives. Although benign and rare, these tumours may rupture and cause death from internal abdominal bleeding. Such lesions have not yet been reported in association with other estrogen or progestagen preparations, but they should be considered if abdominal pain and tenderness, abdominal mass, or shock due to abnormal decrease in the volume of circulating blood occurs in patients receiving estrogen. Liver cell cancerous tumour has also been reported in women taking estrogen-containing oral contraceptives.

Before you use OESCLIM® talk to your doctor or pharmacist if you:

- are taking any non-prescription medicines, including herbal products (St. John’s Wort)
- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- drink alcohol
- smoke
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have a history of high cholesterol or high triglycerides (blood lipids)
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus)
- have a history of depression
- are undergoing surgery or need long bed rest

**ADVERSE EFFECTS**

Like all medications, OESCLIM® may cause side effects. The most frequently reported side effect is redness or irritation under or around the patch. In clinical trials with OESCLIM®, about 3 out of every ten women reported at least one local skin reaction to the patch at some point during their treatment. Out of all the patches applied in these studies, only 4 of every hundred times the patch was applied did reactions occur. These reactions included redness, itching, spots, burning and swelling.

The most commonly reported adverse reaction to OESCLIM® in clinical trials was application site reaction, which included redness, itching, spots, burning and swelling. Of the 22,239 applications in three clinical studies, 1,017 (4.6%) patches became detached. The second most frequent adverse reactions were symptoms of specific estrogen therapy intolerance, reported by 48.6% of patients in clinical trials. Approximately 30% of patients experienced signs of elevated estrogen levels, such as pain in the breast, irregular bleeding between periods and spotting.

The following effects have been reported in women using estrogens (these include estrogens used for birth control). Check with your doctor if these symptoms become troublesome.

- Nausea
- retention of fluid
- migraine headaches
- localized darkening of the skin
- breast tenderness and excessive vaginal secretions (may be a sign that too much estrogen is taken)
- persistent upper abdominal pain, nausea, vomiting, tender abdomen (may be signs of gallbladder disease)
- easy bruising, excessive nose bleeds, excessive heavy periods (may be signs of abnormal clotting)
- lower abdominal pain or swelling, painful and/or heavy periods (may be signs of growth of fibroids in the uterus)
- yellowing of the eyes or skin (may be signs of jaundice)
- upper abdominal pain or swelling (may be signs of liver tumours)

Check with your doctor as soon as possible if any of the following occur:

- irregular vaginal bleeding
- intolerable breast tenderness
• breast enlargement or lumps
• pain or heaviness in the legs or chest
• severe headaches
• dizziness
• changes in vision
• persistent or severe skin irritation
• fluid retention or bloating persisting for more than 6 weeks

Check with your doctor immediately if you experience:

• narrowing of the throat
• sudden shortness of breath
• tightness of the chest or trouble breathing
• coughing blood
• rapid pulse or dizziness
• tender or painful inflammation of the veins
• pain or heaviness in the legs or chest
• any other unusual symptom

**HOW TO USE OESCLIM®**

Your doctor will explain when to start using OESCLIM®. The OESCLIM® patches are applied twice weekly on the same days of each week. The system is changed every 3 or 4 days.

OESCLIM® is usually applied for 25 days out of 28 followed by 2 to 7 treatment-free days. Therefore 7 patches are required per cycle. To help you, we have included a timetable that marks the days of the week on which you should change your patch and the day you should remove the 7th patch (25th day of the cycle). Your next cycle starts with the next patch application.

If you still have your uterus, your doctor should prescribe another hormone drug (a progestogen) at the same time as the patch for at least the last 12 days of each treatment cycle with OESCLIM®.

Bleeding similar to menstrual bleeding may occur during the treatment-free period. This bleeding should be normal and slight.

Your doctor may prescribe the treatment using a different schedule that is better adapted to your condition. The system may be applied continuously with no treatment-free days.
It is important that you take your medication as your doctor has prescribed. Do not discontinue or change your therapy without consulting your doctor.

**How OESCLIM® Works**

Estradiol is the main estrogen produced by your ovaries prior to the menopause, and is the same estrogen that is in OESCLIM®. When applied to the skin, the OESCLIM® patch continuously releases small, controlled quantities of estradiol, which passes through your skin and into your bloodstream. The amount of estrogen prescribed depends on your body’s needs. Your doctor may adjust the amount you get by prescribing another (different) patch size.

By providing estradiol, OESCLIM® offers relief from menopausal symptoms.

**How and Where to Apply OESCLIM®**

The site of application should be changed each time the patch is applied. However, each time you apply the patch you should always apply it to the same area of your body (i.e., if the patch is applied to the buttocks, move the patch from the right side to the left side).

1. **Preparing the skin:** In order for the patch to stick, the skin should be clean, dry and free of creams, lotions or oils. If you wish, you may use body lotion after the patch has been properly applied to the skin. The skin should not be irritated or broken, since this may alter the amount of hormone you get. Contact with water (bath, pool or shower) will not affect the patch, although very hot water or steam may loosen it and therefore should be avoided (see Helpful Hints).

2. **Where to Apply the OESCLIM® Patch:** The patch may be applied to the buttock, the torso (area under the arms at the elbow level, abdomen) or the upper part of the arm or thigh (see Fig. 1). Change the site of application each time you put a patch on. You can use the same spot more than once but **not twice in a row**.
Do not apply OESCLIM® to your abdomen, if a dose of OESCLIM® has been previously adjusted by your doctor with the patch applied to other sites of your body, as this might change the amount of hormone delivered.

Fig. 1

Avoid areas of the skin where clothing may rub the patch off or areas where the skin is very hairy or folded.

Also avoid areas where the patch is likely to be exposed to the sun since this may affect how the patch works.

Do not apply OESCLIM® to your breast, since this may cause unwanted effects and discomfort.

3. Opening the Pouch: Each OESCLIM® patch is individually sealed in a protective pouch. Tear open this pouch and remove the patch. Do not use scissors, as you may accidentally cut and destroy the patch.

4. Removing the Liner: The patch is made up of an adhesive part containing the active substance and a transparent protective film. The protective liner must be removed.

To separate the patch from the protective liner, lift a corner of the liner and peel it off the patch. Discard the protective liner. Avoid touching the adhesive. Press the sticky side on the skin and smooth down.

Apply the patch immediately after opening the pouch and removing the liner.

5. Applying the OESCLIM® Patch: Apply the adhesive side to the spot you have chosen. Check that the OESCLIM® system is sticking correctly: press firmly in place for about 10 seconds with the palm of your hand over its entire surface area.

6. When and How to Remove the Patch: To remove OESCLIM®, simply lift up one edge and pull. The OESCLIM® patch should be changed twice weekly. Always change it on the same 2 days of the week. If you forget to change it at the scheduled time, there is no
cause for alarm. Just change it as soon as possible and continue to follow your usual schedule.

After you remove the patch fold it in half with the adhesive side inwards. **Throw it away out of the reach of children and pets.**

Apply a new OESCLIM® patch on a different spot of clean, dry skin.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

In the case of overdosage, immediately remove the patch. Contact your doctor and/or your local Poison Control Centre.

**PHARMACEUTICAL INFORMATION**

Like most medicines OESCLIM® contains other substances in addition to estrogen. The other substances are: copolymer of ethylene vinyl acetate, dipropylene glycol, octyl dodecanol, ethyl cellulose, protective films made of foam and silicone-treated polyester.

**STORAGE**

OESCLIM® should be stored at room temperature (15–25°C). Avoid freezing. **Do not store unpouched.** OESCLIM® patches should be kept out of the reach of children and pets before and after use.

**HELPFUL HINTS: WHAT TO DO IF THE PATCH FALLS OFF**

Should a patch fall off in a very hot bath or shower, shake the water off the patch. Dry your skin completely and reapply the patch (to a new area of skin) and continue your regular schedule. If it does not stick, then apply a **new** patch and continue your regular schedule.

If hot baths, saunas or whirlpools are something you enjoy and you find that the patch is falling off, you may consider removing the patch **temporarily** while you are in the water. If you do remove the patch temporarily, the adhesive side of the patch should be placed on the protective liner that was removed when originally applying the patch. Wax paper may be used as an alternative to the liner. This prevents the contents of the patch from emptying by evaporation while you are not wearing it.
In addition to exposure to very hot water, there are some other causes for the patch failing to stick. If you are having patches fall off regularly, this could be happening as a result of:

- using any type of bath oil
- using soaps with a high cream content
- using skin moisturizers before applying the patch

Patch adhesion may be improved if you avoid using these products, and by cleansing the site of application with rubbing alcohol before you apply the patch.

**WHAT TO DO IF YOUR SKIN BECOMES RED OR IRRITATED UNDER OR AROUND THE PATCH**

As with any product that covers the skin for a period of time (such as bandages), the OESCLIM® patch can produce some skin irritation in some women. This varies according to the sensitivity of each woman.

Usually this redness does not pose any health concern to you, but to reduce this problem there are some things you may do:

- choose the buttock as the site of application
- change the site of application of the OESCLIM® patch every time a new patch is applied, usually twice weekly

Experience with OESCLIM® has shown that if you allow the patch to be exposed to the air for approximately 10 seconds after the protective liner has been removed, skin redness may not occur.

If redness and/or itching continues, you should consult your physician.

**ALWAYS REMEMBER**

Your doctor has prescribed OESCLIM® for you after a careful review of your medical needs. Use it only as directed and do not give it to anyone else. Your doctor should re-examine you at least once a year.

**IF YOU HAVE ANY QUESTIONS, CONTACT YOUR DOCTOR OR PHARMACIST.**

**Product Identification**

OESCLIM® 25 micrograms/24 hours: A transdermal system with a surface area of 11 cm² containing 5 mg of estradiol-17β.
OESCLIM® 37.5 micrograms/24 hours: A transdermal system with a surface area of 16.5 cm² containing 7.5 mg of estradiol-17β.

OESCLIM® 50 micrograms/24 hours: A transdermal system with a surface area of 22 cm² containing 10 mg of estradiol-17β.

OESCLIM® 75 micrograms/24 hours: A transdermal system with a surface area of 33 cm² containing 15 mg of estradiol-17β.

OESCLIM® 100 micrograms/24 hours: A transdermal system with a surface area of 44 cm² containing 20 mg of estradiol-17β.

Each system is contained in a heat-sealed paper/aluminium sachet.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrpm@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Health Canada
Tunney’s Pasture, Address Locator: 0701C
Ottawa ON, K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.
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