

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **OESCLIM**[®]

Estradiol-17 β 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.
1600 Notre Dame St. West, Suite 312
Montréal, Québec
H3J 1M1

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OESCLIM®
Estradiol-17β

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Transdermal patch 25, 37.5, 50, 75, 100 mcg/24 hrs	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

OESCLIM® (Estradiol-17β) is indicated for the relief of menopausal and post menopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

OESCLIM® (Estradiol-17β) 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 Dosage Forms, Composition and Packaging 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

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.^{3,30,31}

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) 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.³¹

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) 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.³⁰

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.

WARNINGS AND PRECAUTIONS

General

- 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.
- 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**.

Carcinogenesis and Mutagenesis

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).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.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.³⁰

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease (see **Contraindications**).

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.

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.

Ovarian cancer

Some recent epidemiologic studies have found that the use of hormone replacement therapy (*estrogen-alone* and *estrogen plus progestin* therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular

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.^{6,9,31} 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.^{30,31}

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).³¹

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 (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.³⁰

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.⁹

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.⁶

Blood Pressure

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.

Endocrine and Metabolism

Glucose and lipid metabolism

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 or porphyria need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Calcium and phosphorus metabolism

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.

Hypothyroidism

Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see **Drug-Laboratory Test Interactions**).

Genitourinary

Vaginal bleeding

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

Uterine leiomyomata

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

Endometriosis

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

Hematologic

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) and systemic lupus erythematosus. 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.

Hepatic/Biliary/Pancreatic

Gallbladder Disease

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

Jaundice

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.

Liver function tests

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 **Monitoring and Laboratory Tests**.

Hepatic

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.

Neurologic

Cerebrovascular insufficiency

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication. Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be reevaluated.

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

Renal

Fluid retention

Estrogens with or without progestins may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. 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.

Skin

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.

Monitoring and Laboratory Tests

- 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.**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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

Blood and lymphatic system disorders

Altered coagulation tests (see **Warnings and Precautions, Drug-Laboratory Tests Interactions**).

Cardiac disorders

Palpitations; increase in blood pressure (see **Warnings and Precautions**); coronary thrombosis.

Endocrine disorders

Increased blood sugar levels; decreased glucose tolerance.

Eyes disorders

Neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.

Gastrointestinal disorders

Nausea; vomiting; abdominal discomfort (cramps, pain, pressure); bloating.

General disorders and administration site conditions

Fatigue; changes in appetite; changes in body weight; change in libido.

Hepatobiliary disorders

Gallbladder disorder, asymptomatic impaired liver function; cholestatic jaundice.

Musculoskeletal and connective tissue disorders

Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous System disorders

Aggravation of migraine episodes; headaches; dizziness; neuritis.

Psychiatric disorders

Mental depression; nervousness; irritability.

Renal and urinary disorders

Cystitis; dysuria; sodium retention; edema.

Reproductive system and breast disorders

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

Skin and subcutaneous tissue disorders

Cloasma or melasma, which may persist when drug is discontinued; erythema multiforme; hemorrhagic eruption; loss of scalp hair; hirsutism and acne.

Vascular disorders

Isolated cases of: thrombophlebitis, thromboembolic disorders.

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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.

DRUG INTERACTIONS

Overview

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.

Drug-Drug Interactions

The extent of interference with transdermally administered estradiol-17 β 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.

Drug-Herb Interactions

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.

Drug-Laboratory Interactions

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-17 β , 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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.

Recommended Dose and Dosage Adjustment

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.

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.

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-17 β can be rapidly reduced by removal of the patch. Symptomatic treatment should be given.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Pharmacodynamics

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

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 (C_{max}) are 25, 81 and 108 pg/mL respectively with OESCLIM[®] 25, 50 and 100, and estimated C_{max} 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.

STORAGE AND STABILITY

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage forms / Packaging

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

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

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.

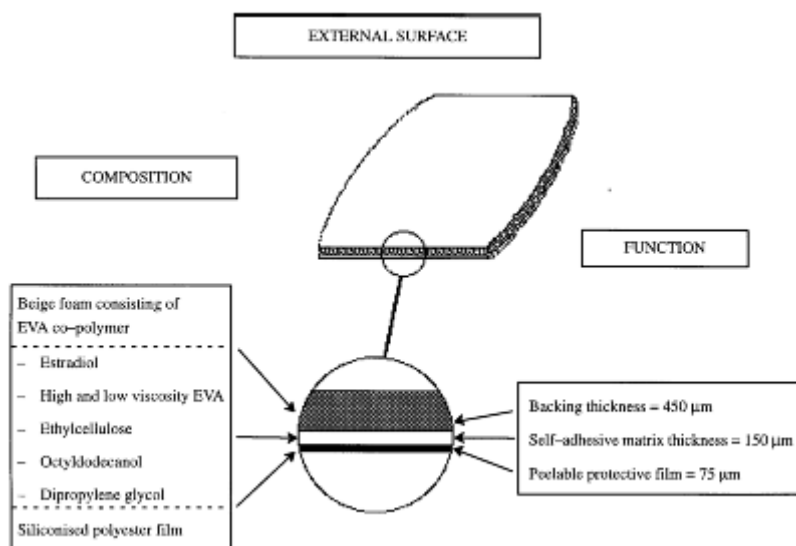
OESCLIM[®] 50: Each rectangular (22 cm²) transdermal system contains estradiol hemihydrate corresponding to 10 mg estradiol for delivery of estradiol 50 mcg/24 hrs. Patient pack of 8 systems.

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.

Composition

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-17 β . 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-17 β 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.

PART II: SCIENTIFIC INFORMATION

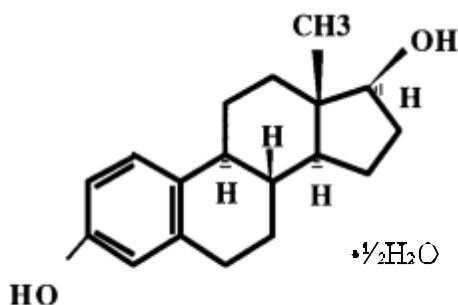
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Estradiol hemihydrate (INN)

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

Structural formula:



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

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.

Study identification	Design	Primary aim	Secondary aims	Population	Evaluated patients	Treatment features
Study #1	Randomized Double-blind 2 parallel groups Placebo-control Multicentre	Efficacy on vasomotor symptoms at 12 weeks	Evaluate: - efficacy on other menopause related symptoms - local skin tolerability - specific tolerability to estrogen therapy - general safety - treatment acceptability.	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	61 OESCLIM® 50: 32 Placebo: 29	Continuous No progestogen Fixed dose: OESCLIM® 50 or placebo 2 systems per week 12 to 13 weeks of treatment

Study identification	Design	Primary aim	Secondary aims	Population	Evaluated patients	Treatment features
Study #2	Uncontrolled Open-label Multicentre	Local skin tolerability over one year	Evaluate specific tolerability to Hormone Replacement Therapy; general safety and efficacy.	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 Natural or surgical menopause	222	24 or 28-day discontinuous or continuous Fixed dose for 3 months: OESCLIM [®] 50, flexible after 3 months: OESCLIM [®] 25, 50 or 100 Total of 12 months of treatment with concomitant progestogen treatment given in sequential fashion during the last 12 to 16 days of cycles
Study #3	Randomized Open-label Multicentre 2 parallel groups Comparison of OESCLIM [®] 50 and Estraderm TTS [®] 50	Local skin tolerability after 16 weeks of treatment.	Compare OESCLIM [®] 50 and Estraderm TTS [®] 50 in terms of efficacy, general tolerability, specific tolerability to estrogen treatment.	Symptomatic menopausal patients with ≥ 1 hot flush and ≥ 1 night sweat during the 7-day self-assessment	281 OESCLIM [®] 50: 143 Estraderm TTS [®] 50: 138	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

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 (β5 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.

	Inclusion Visit	Study Visits			
Study # 1	Baseline (Vi)	After 4 weeks (V1)	After 8 weeks (V2)	After 12 weeks (Vf)	
Mean ± SD	9.31 ± 4.24	1.15 ± 2.14	0.32 ± 1.11	0.26 ± 0.76	
Difference		89.2%	97.6%	97.5%	
Study # 3	Baseline (Vi)	After 4 weeks (V1)	After 8 weeks (V2)	After 12 weeks (V3)	After 16 weeks (Vf)
Mean ± SD	9.95 ± 6.29	2.54 ± 2.94	0.98 ± 2.04	1.11 ± 3.21	0.60 ± 1.61
Difference		71.0%	86.6%	86.3%	91.6%

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

	Inclusion Visit	Study Visits			
Study # 2	Baseline (Vi)	After 2 months (V1)	After 6 months (V2)	After 11 months (V3)	After 12 months (Vf)
Mean ± SD	5.35 ± 4.80	0.47 ± 1.32	0.21 ± 0.54	0.42 ± 1.28	---
Difference		91.2%	96.1%	92.1%	---

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

Study # 1	After 4 weeks (V1)	After 8 weeks (V2)	After 12 weeks (Vf)	
Oesclim 50 (n=28)	12 (42.9%)	20 (71.4%)	24 (85.7%)	
Study # 3	After 4 weeks (V1)	After 8 weeks (V2)	After 12 weeks (V3)	After 16 weeks (Vf)
Oesclim 50 (n=50)	15 (30.0%)	29 (58.0%)	33 (66.0%)	36 (72.0%)

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

Study # 2	After 2 months (V1) (n=136)	After 6 months (V2) (n=100)	After 11 months (V3) (n=83)
Oesclim 50 (n=142)	102 (75.0%)	79 (79.0%)	63 (75.9%)

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.

DETAILED PHARMACOLOGY

Estrogens (naturally occurring, their derivatives or synthetic estrogens) are the basis of post-menopausal 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 µg 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 µg/g and 183 µg/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 µg/day, the urinary conjugates of estradiol and estrone did not exceed 4.2 µg/g and 11.3 µg/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-17 β . 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.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**OESCLIM[®]
Estradiol Transdermal Patch**

IMPORTANT: Read this carefully before you start taking OESCLIM[®] and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about OESCLIM[®].

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

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.

What is OESCLIM[®] used for?

OESCLIM[®] is used to relieve menopausal and postmenopausal symptoms.

These occur when your body does not produce enough estrogen, such as:

- Naturally;
- Following surgery.

If you have a uterus, OESCLIM[®] must be taken with a progestin. Your doctor will prescribe this to you. It is important to take them together as this will help prevent problems with the lining of the uterus such as cell overgrowth (endometrial hyperplasia) and cancer.

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.

How does OESCLIM[®] work?

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.

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 flashes" 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.

What are the ingredients in OESCLIM[®]?

Medicinal ingredients: estradiol

Non-medicinal ingredients: Ethylene/vinyl acetate copolymer, dipropylene glycol, octyl dodecanol, ethylcellulose.

OESCLIM[®] comes in the following dosage forms:

Transdermal patch:

- 25 mcg / 24 hours as a 5 mg patch
- 37.5 mcg / 24 hours as a 7.5 mg patch
- 50 mcg / 24 hours as a 10 mg patch
- 75 mcg / 24 hours as a 15 mg patch
- 100 mcg / 24 hours as a 20 mg patch

Do not use OESCLIM[®] if:

- You are pregnant
- You are breast-feeding

- You are allergic or have unusual reaction to any of the ingredients of OESCLIM[®] (see the list of ingredients above)
- You have or had active liver disease
- You have a personal history of breast cancer or endometrial cancer (cancer of the lining of the uterus)
- You have or had undiagnosed or unusual vaginal bleeding
- You have or had stroke, a heart attack, or a coronary heart disease
- You have or had migraine headaches
- You have active or personal history of venous thromboembolism (blood clots in the large veins or lungs) or thrombophlebitis (inflammation of the veins)
- You have or had partial or complete loss of vision due to blood vessel disease of the eye
- You have or had porphyria (a disease of blood pigment)
- You have or had endometrial hyperplasia (overgrowth of the lining of the uterus)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OESCLIM[®]. Talk about any health conditions or problems you may have, including 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
- have a history of gallbladder disease
- 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
- have been diagnosed with porphyria (a disease of blood pigment)

Other warnings you should know about:

Breast cancer

The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

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.

Ovarian cancer

In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

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

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Abnormal blood clotting

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

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.

Blood pressure

Women using hormonal replacement therapy (HRT) may experience high blood pressure (hypertension). Your doctor will monitor your blood pressure while you are taking OESCLIM.

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. This study indicated an increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in postmenopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

Hepatic

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.

Interactions with this medication

The following may interact with OESCLIM[®]:

- anticoagulant agents;
- antidiabetic agents;
- antihypertensive agents;
- herbal and natural products, like St. John's wort.

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products.

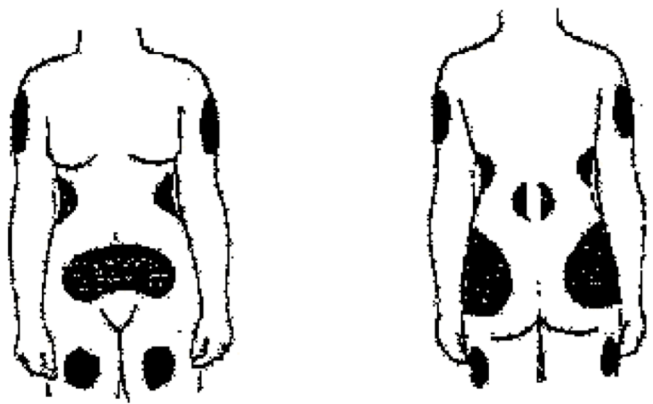
How and where to apply OESCLIM[®]:

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.

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.

Usual dose:

The OESCLIM[®] patch contains estradiol. When applied to the skin as directed above, OESCLIM[®] releases estradiol which passes through the skin and into the bloodstream.

Your doctor will explain when to start using OESCLIM[®]. The OESCLIM[®] patches are applied twice weekly on the same day of each week. You will apply one patch for a three day period and the next patch for a four day period. Therefore, the patch is changed every 3 or every 4 days.

OESCLIM[®] is usually applied for 24 to 28 days followed by 2 to 7 treatment-free days. Your next 24 to 28 day patch treatment cycle starts after your last treatment-free day.

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.

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.

Overdose:

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.

If you think you have taken too much OESCLIM[®], contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using OESCLIM[®]?

These are not all the possible side effects you may feel when taking OESCLIM[®]. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Redness, irritation, itching, discoloration, burning and swelling of skin under or around the patch application site
- Nausea and vomiting
- Abdominal cramps or pain, bloating
- Joint and muscle pain
- Fatigue
- Change in appetite
- Change in weight (increase or decrease)
- Change in libido
- Nervousness and irritability
- Breast pain, breast swelling, vaginal itching, excessive vaginal secretions, irregular bleeding between periods and spotting, painful sexual intercourse
- Lower abdominal pain or swelling and painful and/or heavy periods which may be signs of fibroids in the uterus
- Hair loss, excessive growth of hair on the face or body (hirsutism), acne, skin rash
- Fluid retention
- Melasma: darkening of the skin of the face especially when exposed to the sun
- Intolerance to contact lenses

OESCLIM[®] can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Gallbladder disease: Persistent abdominal pain, abdominal tenderness, nausea and vomiting		✓	
Breast cancer: Breast lump		✓	
Crushing chest pain or chest heaviness			✓
Edema: Swelling of the hand and / or feet		✓	
Thromboembolism / Blood clot: Pain, redness or swelling in the leg or feet that may be warm to the touch			✓
Depression: Persistent sad mood			✓
Blood clot in the lung: Sharp pain in the chest, coughing blood or sudden shortness of breath			✓
Sudden partial or complete loss of vision			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Stroke: Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, paralysis or weakness or numbness in an arm or a leg			✓
Unexpected vaginal bleeding		✓	
Jaundice: Yellowing of the skin or eyes			✓
Fluid retention or bloating persisting for more than 6 weeks		✓	
Palpitations: Irregular heart beat			✓
High blood pressure (hypertension)		✓	
Severe headache or migraine headache		✓	
Dizziness		✓	
Persistent or severe skin infection		✓	
Tender or painful vein inflammation			✓
Rapid swelling of the throat (airway blockage)			✓
Abnormal clotting: Easy bruising, excessive nose bleeding or excessively heavy periods		✓	
Liver tumour: Upper abdominal pain or swelling		✓	
Nerve inflammation: Muscle weakness, numbness, pain or tingling		✓	
Painful or difficult urination	✓		
High blood sugar: Frequent urination, thirst, fatigue	✓		
Aggravation of epilepsy: Seizures occurring more often than usual or more severe seizures		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

OESCLIM[®] should be stored at room temperature (15–25°C). Avoid freezing. **Do not store unpouched.** Apply immediately upon removal from the protective pouch. OESCLIM[®] patches should be kept out of the reach of children and pets before and after use. After removal of the patch fold it in half, with the adhesive side inwards, before discarding.

Keep out of reach and sight of children.

If you want more information about OESCLIM[®]:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; Searchlight Pharma website (<http://searchlightpharma.com>), or by calling 514-613-1513.

This leaflet was prepared by:

Searchlight Pharma Inc.
Montréal, Québec H3J 1M1
1-855-331-0830

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