

PRODUCT MONOGRAPH

Pr **SANDOZ ESTRADIOL DERM 50, 75 and 100**
Estradiol hemihydrate (Estradiol-17 β)
Transdermal Therapeutic System

4, 6 and 8 mg estradiol patches
corresponding to
50 mcg/day, 75 mcg/day and 100 mcg/day delivery

Estrogen

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Pr SANDOZ ESTRADIOL DERM 50, 75 and 100

Estradiol hemihydrate (Estradiol-17 β)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Patch/50 mcg, 75 mcg and 100 mcg	Acrylic polymers and tocopherol contained on a polyethylene terephthalate film For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

INDICATIONS AND CLINICAL USE

Sandoz Estradiol Derm (estradiol-17 β) is indicated for the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

Sandoz Estradiol Derm is also indicated for the prevention of osteoporosis in naturally occurring or surgically-induced estrogen-deficiency states in addition to other important therapeutic measures such as adequate diet, calcium and vitamin D intake, cessation of smoking and regular physical weight bearing exercise. The use of Sandoz Estradiol Derm in the prevention of osteoporosis should be considered in light of other available therapies (*see Boxed Warnings*).

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

Geriatrics (>65 years of age):

No clinical studies were conducted to evaluate the effect of Sandoz Estradiol Derm on women more than 65 years old.

Pediatrics:

Sandoz Estradiol Derm should not be used in children.

CONTRAINDICATIONS

Sandoz Estradiol Derm (estradiol-17 β) should not be administered to patients with any of the following conditions:

- Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer).
- Hypersensitivity to this drug or any ingredient in the formulation or component of the patch. For a complete listing, see Dosage Forms, Composition and packaging section.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Endometrial hyperplasia.
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy.
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis.
- Partial or complete loss of vision from ophthalmic vascular disease.
- Porphyria.
- Classical migraine.
- Lactation.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (N=16608) and oral *estrogen-alone* therapy (N=10739) in postmenopausal women aged 50 to 79 years.^{7, 51, 56}

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.⁵⁶

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.⁵¹

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.
- For the prevention of osteoporosis, Sandoz Estradiol Derm should be considered in light of other available therapies.

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 10000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT *versus* 30 on placebo).⁵⁶

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.⁷

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.⁵¹

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 a 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 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 and Endometrial Carcinoma

Estrogen-only HRT increases the risk of endometrial hyperplasia/carcinoma if taken by women with intact uteri. Estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. The incidence of endometrial hyperplasia/carcinoma is reported to be lowered with sequential co-administration of a progestin.

Ovarian cancer

Some recent epidemiologic studies have found 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.

Hepatocellular Carcinomas

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.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Study (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.^{23, 25, 56} 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^{51, 56}.

WHI Trial Findings

In the combined *estrogen plus progestin* arm of the WHI trial, among 10000 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).⁵⁶

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10000 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 CHD⁵¹.

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 oral 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 years²⁵. 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 CHD²³.

Blood Pressure

Women using hormone replacement therapy 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 may have to be discontinued.

Ear/Nose/Throat

Otosclerosis

Estrogens should be used with cautions in patients with otosclerosis.

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 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 in patients with renal insufficiency.

Hypothyroidism

Patients who require thyroid hormone replacement therapy and who are 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 10000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.⁵⁶

In the *estrogen-alone* arm of the WHI trial, among 10000 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 embolism⁵¹.

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), severe obesity (body mass index $>30 \text{ kg/m}^2$) 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

Benign Hepatic Adenomas

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

Gallbladder Diseases:

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

Hepatic Hemangiomas

Particular caution is indicated in women with hepatic hemangiomas, as estrogen may cause an exacerbation of this condition.

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**.

Immune

Angioedema

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

Systemic lupus erythematosus

Particular caution is indicated in women with systemic lupus erythematosus.

Neurologic

Cerebrovascular Insufficiency

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

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 (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline^{43, 44}.

In the *estrogen plus progestin* arm of the WHIMS (N= 4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT *versus* 22 on placebo)⁴³.

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 10000 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 significance⁴⁴.

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 10000 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)⁴⁴.

Epilepsy

Particular caution is indicated in women with epilepsy, as estrogen, with or without progestins, may cause an exacerbation of this condition.

Renal

Fluid Retention

Estrogens may cause fluid retention.

Therefore, particular caution is indicated in cardiac or renal dysfunction, 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

Contact Sensitization

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.

Special Populations

Pregnant Women: Sandoz Estradiol Derm must not be used during pregnancy. Both estrogens and progestins may cause foetal harm when administered to a pregnant woman.

Nursing Women: Sandoz Estradiol Derm must not be used while breastfeeding.

Pediatrics: Sandoz Estradiol Derm should not be used in children.

Geriatrics (>65 years of age): No clinical studies were conducted to evaluate the effect of Sandoz Estradiol Derm on women more than 65 years old.

Monitoring and Laboratory Tests

Before Sandoz Estradiol Derm is administered, the patient should have a complete physical examination including blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only 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 of at least once

a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

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 estrogen/progestin combination in general:

Blood and Lymphatic System Disorders: Altered coagulation tests (see **DRUG INTERACTIONS, 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.

Eye 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, pressure, pain, 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;

premenstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

Skin and Subcutaneous Tissue Disorders: Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism and acne.

Vascular Disorders: Isolated cases of Thrombophlebitis; thromboembolic disorders.

Less Common Clinical Trial Adverse Drug Reactions

The most commonly reported adverse reaction to the estradiol-17 β patch in clinical trials in patients treated for postmenopausal symptoms was redness and irritation at the application site. This caused approximately 0.8% of the patients to discontinue therapy.

Post-Market Adverse Drug Reactions

Adverse events reported from marketing experience include: reports of gastrointestinal disorders, such as, dysguesia, mouth coated, tongue coated; reports of general disorders and administration site conditions, such as, application site rash, application site pruritus and drug ineffectiveness; and reports of skin and subcutaneous tissue disorders, such as, erythema, pruritus, rash, rash vesicular, scars, skin irritation skin burning sensation and skin reaction.

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

DRUG INTERACTIONS

Overview

- Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.
- Preparations inducing liver enzymes, (e.g. barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

Drug-Drug Interactions

The following section contains information on drug interactions with ethinyl estradiol containing products (specifically, oral contraceptives) that have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens. Therapeutic monitoring is recommended.

Table 2: Potential Drug-Drug Interactions

Proper name	Effect
Anticonvulsants (phenobarbital, phenytoin and carbamazapine)	↑ metabolism of ethinyl estradiol. ↓ plasma concentrations of estradiol.
Acetaminophen	↑ AUC and/or plasma concentrations of ethinyl estradiol. ↓ plasma concentrations of acetaminophen
Ascorbic acid	↑ AUC and/or plasma concentrations of ethinyl estradiol
Atorvastatin	↑ AUC values for ethinyl estradiol by 20%
Clofibrilic acid	↑ clearance of clofibrilic acid
Cyclosporin	↑ plasma concentrations of cyclosporin
Morphine	↑ clearance of morphine
Prednisolone	↑ plasma concentrations of prednisolone
Rifampin*	↑ metabolism of ethinyl estradiol. ↓ plasma concentrations of estradiol.
Salicylic acid	↑ clearance of salicylic acid
Temazepam	↑ clearance of temazepam
Theophylline	↑ plasma concentrations of theophylline
Troglitazone	↓ plasma concentrations of ethinyl estradiol by 30%

* Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Drug-food interactions

The interaction of Sandoz Estradiol Derm with food has not been studied.

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 might interfere with steroid metabolism and therefore alter the 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, obtained from the widely spread health stores.

Drug-Laboratory Test 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; 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.
- increased serum triglyceride and phospholipid concentration.
- The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.
- The pathologist should be informed that the patient is receiving HRT therapy when relevant specimens are submitted.

Drug-lifestyle interactions

Acute alcohol ingestion during HRT may lead to elevations in circulating estradiol levels.

DOSAGE AND ADMINISTRATION

Dosing Considerations

In women who are not currently taking oral estrogens, treatment with Sandoz Estradiol Derm (estradiol-17 β) can be initiated at once. In women who are currently taking oral estrogens, treatment with Sandoz Estradiol Derm can be initiated on reappearance of menopausal symptoms, following discontinuation of oral therapy.

Sandoz Estradiol Derm should be applied twice weekly i.e. the patch should be changed once every 3 to 4 days.

Cyclical administration is recommended (21 to 25 days of therapy followed by 5 to 7 days without). Continuous non-cyclic 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 intact uteri, a progestin should be sequentially co-administered for a minimum of 12 to 14 days per cycle to avoid over stimulation of the endometrium and endometrial hyperplasia/carcinoma. The addition of sufficient progestin to induce secretory transformation of the endometrium during estrogen replacement therapy is mandatory.

For all therapeutic indications, the lowest effective dose should be used for maintenance therapy.

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

Progestin therapy is not generally required in women who have had a hysterectomy.

Recommended Dose and Dose Adjustment

Menopausal Symptoms

Treatment of menopausal symptoms is usually initiated with a patch that releases 50 mcg estradiol-17 β /day i.e. Sandoz Estradiol Derm 50. Thereafter the dosage should be adapted to the needs of the individual.

Breast discomfort, breakthrough or heavy vaginal bleeding, water retention, bloating or nausea (if persisting for more than six weeks), are generally signs that the estrogen dose is too high and needs to be lowered. If on the other hand, the selected dose fails to eliminate the signs and symptoms of estrogen deficiency, a higher dose may be considered.

For maintenance therapy one should always use the lowest dose that still proves effective. The requirement for hormone replacement therapy for menopausal symptoms should be reassessed periodically. Attempts to taper or discontinue the medication should be made at 3- to 6-month intervals.

Prevention of Postmenopausal Osteoporosis

For optimal prevention of postmenopausal bone loss in women for whom the drug is indicated, therapy should be initiated as soon as possible after diagnosis of menopause. The dosage of estradiol-17 β may require adjustment according to the patient's clinical status, the plasma estradiol-17 β levels and the results of bone mineral density studies. Ideally, plasma estradiol-17 β levels should be maintained at 183 pM/L (50 pg/mL).

Discontinuation of hormone replacement therapy may re-establish the natural rate of bone loss.

Missed dose

Patients, who miss applying a patch, should apply a new patch as soon as possible. The subsequent patch should be applied according to the original treatment schedule.

Administration

Patch Application

The physician should discuss the most appropriate placement of the patch with the patient. Immediately after removal of a patch from the pouch and removal of the protective liner, the adhesive side of the Sandoz Estradiol Derm patch should be placed on a clean, dry area of intact skin. The area selected should not be oily, damaged or irritated, and not exposed to the sun. The site selected should also be one at which little wrinkling of the skin occurs during movement of the body, preferably the buttocks, lower abdomen or hip. The patch may also be placed on the side or lower back.

The patch should be placed consistently on the same area of the body with each application (i.e. either the buttocks, lower abdomen, hip, side or lower back). Experience to date has shown that less irritation of the skin occurs on the buttocks than on other sites of application. Therefore, it is advisable to apply Sandoz Estradiol Derm to the buttocks. The waistline should be avoided, since tight clothing may dislodge the patch. The patch should be pressed firmly in place with the palm of the hand, making sure there is good contact, especially around the edges. In the event that a patch should fall off, it can be reapplied. If it fails to adhere then a new patch may be applied. In

either case, the original treatment schedule should be continued. Patches should not be applied to the same skin site twice in succession.

Sandoz Estradiol Derm must not be applied to the breasts to avoid potentially harmful effects on the breast tissue.

Co-administration of Progestins

Sandoz Estradiol Derm should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. Progestin therapy is not required as part of hormone replacement therapy in women who have had hysterectomy.

OVERDOSAGE

Symptoms of Overdose

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

Treatment of Overdose

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 suspected drug overdose, contact your regional Poison Control Centre.

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Sandoz Estradiol Derm is designed to deliver daily estradiol-17 β , a physiologic hormone, transdermally into the systemic circulation. Due to the transdermal route of administration, the estradiol-17 β does not undergo first-pass liver metabolism. Resultant estradiol-17 β plasma levels are comparable to those seen in pre-menopausal women in the early follicular phase of the menstrual cycle. Estradiol-17 β stimulates target tissues such as the uterus, breast and vagina.

Pharmacodynamics

Hormone Replacement Therapy

Sandoz Estradiol Derm provides continuous controlled transdermal delivery of estradiol-17 β such that estradiol-17 β levels as well as the E₂/E₁ ratio in postmenopausal women are restored to those seen in the early follicular phase of the pre-menopausal range. Sandoz Estradiol Derm thus alleviates the symptoms of estradiol-17 β deficiency in menopausal women.

Pharmacokinetics

Absorption

Studies in postmenopausal women using estradiol-17 β patches which provide 50, 75 and 100 mcg of exogenous estradiol-17 β per day, showed increased blood levels within 4 hours. These levels

were linearly proportional to the size of the dose and maintained respective mean serum estradiol-17 β levels of 173, 217 and 308 pM/L (47, 59 and 84 pg/mL) above baseline (typically 37 pM/L). At the same time, increases in estrone serum concentration averaged only 111, 81 and 207 pM/L (30, 22 and 56 pg/mL) above baseline, respectively, providing an average E₂/E₁ ratio between 1.6 and 2.7, well within the pre-menopausal range.

Distribution

Mean plasma clearance rates of estradiol-17 β and estrone in women have been estimated to be 735 L/day per m² and 1 213 L/day per m², respectively. Hence, based on studies with estradiol-17 β patches, for women with a body surface area of 1.4-1.9 m², (weight, 48-86 kg; average height 157 cm) estradiol-17 β patches which provide 50, 75 and 100 mcg/day should maintain mean steady-state serum concentration as follows:

Patch	Estradiol Dosage (mcg per day)	Expected Increase in Serum Levels of Estradiol (pM/L) Above Baseline (typically 37 pM/L)
Estradiol 50	50	88-147
Estradiol 75	75	132-228
Estradiol 100	100	176-312

Estradiol-17 β delivered by the transdermal route result in an E₂/E₁ ratio of approximately 1.

Metabolism

Metabolism and plasma levels of estradiol-17 β delivered transdermally are similar to those in pre-menopausal women.

Serum concentrations of estradiol-17 β and estrone returned to pre-application levels within 24 hours after removal of the patch.

Excretion

Estradiol-17 β is rapidly metabolized, primarily in the liver and gut. Its most important metabolites are estriol and estrone and their conjugates (glucuronides, sulphates); these are far less active than estradiol-17 β . The bulk of the metabolites is excreted in the urine as glucuronides and sulphates. Estrogen metabolites are also subject to enterohepatic circulation. The skin metabolizes estradiol-17 β only to a small extent.

The daily urinary output of estradiol-17 β conjugates increased 3 to 10 times the baseline values and returned to near baseline within 2 days after removal of the patch. Multiple-application studies yielded similar results, with urinary output of estradiol-17 β conjugates returning to baseline within 3 days of patch removal.

The plasma elimination half-life of estradiol-17 β permits a rapid cessation of estrogen therapy. The plasma elimination half-life of estradiol-17 β is approximately 1 hour.

Special Populations and Conditions

Geriatrics (>65 years of age)

No clinical studies were conducted to evaluate the effect of Sandoz Estradiol Derm on women more than 65 years old.

Pediatrics

Sandoz Estradiol Derm should not be used in children.

Gender

Sandoz Estradiol Derm should be used in women only.

Estrogen Pharmacology

Estradiol-17 β is the major estrogenic hormone secreted by the human ovary. Among numerous effects, estradiol-17 β is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. It promotes growth and development of the vagina, uterus, fallopian tubes, and breasts. Estradiol-17 β contributes to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and to the pigmentation of the nipples and genitals. Estradiol-17 β also affects the release of pituitary gonadotropins.

After menopause, when the ovaries have ceased to function, only small amounts of estradiol-17 β are still produced, i.e. from the aromatization of androstenedione to estrone and to a lesser extent, testosterone to estradiol-17 β . Estrone is transformed to estradiol-17 β by the enzyme 17 β -hydroxysteroid-dehydrogenase. Both enzymes prevail in fat, liver and muscle tissue.

In pre-menopausal women, the ratio of estradiol-17 β (E₂) to estrone (E₁) (i.e. E₂/E₁ ratio) in the plasma is in the range of 0.5 to 2, depending on the phase of the menstrual cycle. The E₂/E₁ ratio for untreated postmenopausal women is below 0.5.

Loss of ovarian estradiol-17 β production after menopause can result in the following: instability of thermoregulation causing hot flushes associated with sleep disturbance and excessive sweating; accelerated loss of bone matrix and mineral; alterations in lipid metabolism; urogenital atrophy, causing dyspareunia and urinary incontinence.

The protection against endometrial hyperplasia/carcinoma in women with intact uteri is necessary during long-term therapy.

Published data suggest that 12 to 14 days of sequential progestin treatment during estrogen replacement therapy reduces the occurrence of endometrial hyperplasia, and thereby irregular bleeding and endometrial carcinoma, compared to estrogen treatment alone.

STORAGE AND STABILITY

Store patches between 15 and 30°C. Protect from freezing.

Each patch is individually sealed in a separate pouch. Do not store out of the pouch. Apply immediately upon removal from the protective pouch.

Keep Sandoz Estradiol Derm out of reach of children and pets both before use and when disposing of used patches.

Special handling instructions

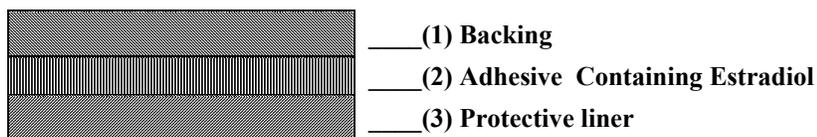
See **DOSAGE AND ADMINISTRATION**-Patch Application section.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Estradiol Derm (estradiol-17 β) is a thin, oval, multilayer, transparent transdermal therapeutic system, i.e. an adhesive patch, containing estradiol-17 β , that is designed for application to an area of intact skin.

The Sandoz Estradiol Derm patch comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are:

- A flexible transparent backing film of polyethylene terephthalate.
- An adhesive formulation containing estradiol-17 β , acrylic copolymers and tocopherol concentrate.
- A transparent protective liner of polyester that is attached to the adhesive surface and must be removed before the patch can be used.



The active component of the patch is estradiol-17 β . The matrix provides a source for continuous delivery of drug for up to 4 days.

Sandoz Estradiol Derm is available in three strengths; the composition per unit area in each strength is identical.

Supplied

Sandoz Estradiol Derm 50 mcg: Each thin, oval; multilayer, transparent, 20 cm² transdermal therapeutic system, contains: 4.1 mg of estradiol hemihydrate equivalent to 4 mg of estradiol-17 β for continuous delivery of 50 mcg/day. Non-medicinal Ingredients: acrylic copolymer and d- α -tocopherol.

Available in patient packs of 8 patches.

Sandoz Estradiol Derm 75 mcg: Each thin, oval, multilayer, transparent, 30 cm² transdermal therapeutic system, contains: 6.2 mg of estradiol hemihydrate equivalent to 6 mg of estradiol-17 β

for continuous delivery of 75 mcg/day. Non-medicinal ingredients: acrylic copolymer and d- α -tocopherol.

Available in patient packs of 8 patches.

Sandoz Estradiol Derm 100 mcg: Each thin, oval, multilayer, transparent, 40 cm² transdermal therapeutic system contains: 8.3 mg of estradiol hemihydrate equivalent to 8 mg of estradiol-17 β for continuous delivery of 100 mcg/day. Non-medicinal ingredients: acrylic copolymer and d- α -tocopherol.

Available in patient packs of 8 patches.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

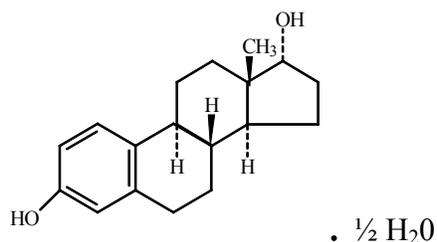
Drug Substance

Proper Name: Estradiol hemihydrate

Chemical Name: estra-1,3,5 (10)-triene-3,17 β -diol

Molecular Formula: $C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$

Structural Formula:



Molecular Weight: 281.4

Description: White crystalline powder

CLINICAL TRIALS

Pivotal comparative bioavailability studies

The following data (corrected for endogenous concentrations) was derived from the comparative bioavailability study, comparing Sandoz Estradiol Derm (0.1 mg estradiol/day) to VivelleTM 100 \blacktriangle (0.1 mg estradiol/day) estradiol transdermal systems in healthy post-menopausal and oophorectomized women:

Table 1: Table of Pharmacokinetic Parameters - Corrected for Baseline Concentration

Estradiol-17 β (0.1 mg/day) From measured data			
Geometric Mean and Arithmetic Mean (CV) (N=61)			
Parameter	Sandoz Estradiol Derm 0.1 mg/day	Vivelle™ 0.1 mg/day	Ratio of Geometric Means (%) (CI)
AUC ₀₋₉₆ (pg·h/mL)	8447.70 9661.8 (53.6%)	6655.55 7507.1 (49.8%)	115.3 (107.5-123.7%)
AUC ₀₋₁₀₈ (pg·h/mL)	8697.78 9967.4 (54.0%)	6864.60 7733.9 (49.4%)	115.0 (107.1-123.4%)
C _{MAX} (ng/mL)	155.071 176.94 (55.4%)	124.589 141.14 (54.4%)	122.9
T _{MAX} (h)*	23.057 (56.9%)	21.089 (53.1%)	--
CSS _{av} (pg/mL)*	100.64 (53.6%)	78.20 (49.8%)	-

* Arithmetic means presented.

▲ Although Vivelle™ is not currently marketed in Canada, Sandoz Estradiol Derm was approved based on clinical studies with Vivelle™.

Further clinical trial data are not available.

Prevention of Osteoporosis

Efficacy and safety of the estradiol-17 β transdermal system in the prevention of postmenopausal osteoporosis have been studied in a 2-year double-blind, randomized, placebo-controlled, parallel group study. A total of 261 hysterectomized (161) and non-hysterectomized (100), surgically or naturally menopausal women (within 5 years of menopause), with no evidence of osteoporosis (lumbar spine bone mineral density within 2 standard deviation of average peak bone mass, i.e. ≥ 0.827 g/cm²) were enrolled in this study; 194 patients were randomized to one of the four doses of estradiol-17 β (100, 50, 37.5 or 25 mcg/day) and 67 patients to placebo. Over 2 years, study systems were applied to the buttock or the abdomen twice a week. Non-hysterectomized women received oral medroxyprogesterone acetate (2.5 mg/day) throughout the study.

The study population comprised naturally (82%) or surgically (18%) menopausal, hysterectomized (61%) or non-hysterectomized (39%) women with a mean age of 52.0 years (range 27 to 62 years; the mean duration of menopause was 31.7 months (range 2 to 72 months). Two hundred thirty nine (92%) of randomized subjects (178 on active drug, 61 on placebo) contributed data to the analysis of percent change from baseline in bone mineral density (BMD) of the AP lumbar spine, the primary efficacy variable. There was an increase in BMD of the AP lumbar spine in all estradiol-17 β dose groups; in contrast to this a decrease in AP lumbar spine BMD was observed in placebo patients. All estradiol-17 β doses were significantly superior to placebo ($p < 0.05$) at all time points with the exception of estradiol-17 β 50 mcg/day at 6 months, implying bone preservation for all treatment groups, as opposed to bone loss for placebo.

Analysis of percent change from baseline in femoral neck BMD also showed similar results; all doses of estradiol-17 β were significantly superior to placebo ($p < 0.05$) at 24 months.

Serum osteocalcin (a marker of bone formation) and urinary excretion of cross-link-N telopeptides of type 1 collagen (a marker of bone resorption) generally decreased in active treatment groups, suggesting a decrease in bone turnover. However, the differences were not statistically significant.

Further clinical trial data are not available.

DETAILED PHARMACOLOGY

See Action and Clinical Pharmacology (Part I)

TOXICOLOGY

Preclinical safety data

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

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PART III: CONSUMER INFORMATION

Pr SANDOZ ESTRADIOL DERM 50, 75 and 100 Estradiol hemihydrate (Estradiol-17 β)

This leaflet is part III of a three-part "Product Monograph" published when Sandoz Estradiol Derm was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Sandoz Estradiol Derm. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Sandoz Estradiol Derm is approved for use in the following situations:

- The Relief of Menopausal and Postmenopausal Symptoms
- To Prevent Osteoporosis
Some women are more likely to develop osteoporosis after menopause than others. You should discuss risk factors for osteoporosis with your doctor.

If you have been prescribed Sandoz Estradiol Derm only for the prevention of osteoporosis you should discuss other therapies with your doctor.

In addition, you should discuss adequate diet, calcium and vitamin D intake, cessation of smoking and regular physical weight-bearing exercise with your doctor or pharmacist.

- Uses of Progestins
If you have not had a hysterectomy (surgical removal of the uterus), estrogens should be prescribed in association with a progestin medication.

Sandoz Estradiol Derm 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 pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. 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 regularly talk with your doctor about whether you still need treatment with HRT.

What it does:

Sandoz Estradiol Derm (estradiol-17 β) is a type of treatment known as hormone replacement therapy (HRT). Sandoz Estradiol Derm is a patch which contains the estrogen hormone, estradiol. Estradiol is an estrogen produced by your ovaries before menopause (the end of monthly menstrual periods).

When applied to the skin, the Sandoz Estradiol Derm patch continually releases small, controlled quantities of estradiol, which pass through your skin and into your bloodstream

Your body normally makes estrogens and progestins (female hormones) mainly in the ovaries. Between ages 45 and 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 suffer 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 flushes**). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms.

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. In osteoporosis, the bones of the spine, wrists and hips break most often. The bones of both men and women start to thin after about age 40, but women lose bone faster after menopause. Using estrogens after menopause slows down bone thinning and may prevent bones from breaking.

When it should not be used:

Sandoz Estradiol Derm (estradiol-17 β) should not be used if you:

- have active liver disease.
- have a personal history of or currently have breast cancer or endometrial cancer (cancer of the uterus) or any other cancer which is sensitive to estrogens.
- have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus).
- have experienced undiagnosed or unexpected genital bleeding.
- have been diagnosed with porphyria (a disease of blood pigment).
- are pregnant or suspect you may be pregnant (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 doctor at this time. If you take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.)
- are breast feeding.
- have a history of coronary heart disease (including heart attack) or stroke.
- experience migraine headaches.
- have a history of or currently have blood clots.
- have active thrombophlebitis (inflammation of the veins).
- have had partial or complete loss of vision due to blood vessel disease of the eye.
- have had an allergic or unusual reaction to Sandoz Estradiol Derm or to any of its components. (See **What the medicinal ingredient is:** and **What the nonmedicinal ingredients are:**)

What the medicinal ingredient is:

Sandoz Estradiol Derm contains the estrogen hormone, estradiol.

What the nonmedicinal ingredients are:

The other substances are acrylic copolymers and tocopherol contained on a polyethylene terephthalate film.

What dosage forms it comes in:

Sandoz Estradiol Derm patch is available in 3 doses:
 Sandoz Estradiol Derm 50 for continuous delivery of 50 mcg of estradiol per day.
 Sandoz Estradiol Derm 75 for continuous delivery of 75 mcg of estradiol per day.
 Sandoz Estradiol Derm 100 for continuous delivery of 100 mcg of estradiol per day.

The dose of Sandoz Estradiol Derm will be based on the reason for its use, as determined by your doctor. (Please see the section called **HOW TO USE Sandoz Estradiol Derm**).

WARNINGS AND PRECAUTIONS

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.

Breast Cancer

The results of the WHI trial indicated an increased risk of breast cancer in postmenopausal 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 postmenopausal 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 (HRT).

Women should have a mammogram (breast x-ray) 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 postmenopausal 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 generally required in women who have had a hysterectomy.

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.

Heart Disease and Stroke

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal 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.

Gallbladder Disease

The use of estrogens by postmenopausal women has been reported to increase the risk of gallbladder disease requiring surgery.

Dementia

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and 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.

BEFORE you use Sandoz Estradiol Derm talk to your doctor or pharmacist if you:

- 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 migraine headache.
- have a personal or family history of blood clots, or a personal history of heart disease or stroke.
- are undergoing surgery or need long bed rest.
- have been diagnosed with porphyria (a disease of blood pigment).
- are pregnant or may be pregnant.
- are breast feeding.
- have had a hysterectomy (surgical removal of the uterus).
- have a history of uterine fibroids or endometriosis.
- smoke.
- have a history of kidney disease, asthma or epilepsy (seizures).
- have a history of liver disease or liver tumours, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy.
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus).
- have a history of high blood pressure.
- have been diagnosed with diabetes.
- have a history of high cholesterol or high triglycerides.
- have a history of depression.
- have been told that you have a condition called hereditary angioedema or if you have had episodes of rapid swelling of the hands, feet, face lips, eyes, tongue, throat (airway blockage), or digestive tract.

- have been diagnosed with lupus.
- have been diagnosed with hearing loss due to otosclerosis.

Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

INTERACTIONS WITH THIS MEDICATION

Some medications can interfere with the action of Sandoz Estradiol Derm and Sandoz Estradiol Derm can interfere with the action of other medications.

Tell your doctor or pharmacist if you are taking any other medications including, prescription medications, over-the-counter medications, vitamins or herbal products. This particularly includes the following: anti-anxiety medicines (e.g. barbiturates, meprobamate), anti-epileptic medicines (.g. phenol barbital, phenytoin or carbamazepine), an anti-inflammatory medicine called phenylbutazone, antibiotics and other anti-infective medicines (e.g. rifampicin, rifabutin, vevirapine, efavirenz), and herbal medicines (e.g. St John's Wort).

PROPER USE OF THIS MEDICATION

Usual dose:

HOW TO USE Sandoz Estradiol Derm

Your doctor will explain when to start using Sandoz Estradiol Derm. The Sandoz Estradiol Derm patches are applied twice weekly on the same days of each week. Each patch should be worn continuously for 3 to 4 days. The dose of Sandoz Estradiol Derm will be based on the reason for its use, as determined by your physician. Your physician may adjust the dosage based on your response to treatment.

Estrogen is usually taken in a cyclic fashion (although your physician's instructions may be different depending upon your personal situation). This means that you would take estrogen on the first 21 or 25 days of the cycle, followed by 5 to 7 days without. Your next cycle starts with the next patch application.

Each box contains eight Sandoz Estradiol Derm patches. If your treatment is for less than 28 days of estrogen (cyclical therapy), you will have 1 or 2 patches leftover which can be used for the next month.

It is important that you take your medication as your physician has prescribed. Do not discontinue or change your therapy without consulting your physician first. You should talk regularly with your physician about how long you will need treatment with estrogen.

How and Where to Apply Sandoz Estradiol Derm

It is recommended that you change the site of application each time the patch is applied. However, each time you apply a 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 right side to left side, twice a week or more if there is any redness under the patch).

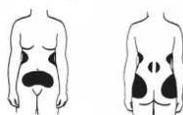
Preparing the Skin

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) won't affect the patch, although very hot water or steam may loosen it and therefore should be avoided (see **Helpful Hints**).

Where to Apply the Sandoz Estradiol Derm Patch

The buttock is the preferred place to apply the patch. Other suitable application sites are the sides, hip, lower back or lower abdomen. 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**.

Figure #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 Sandoz Estradiol Derm to your breast, since this may cause unwanted effects and discomfort.

Opening the Pouch

Each Sandoz Estradiol Derm patch is individually sealed in a protective pouch. Tear open this pouch at the indented notch and remove the patch. Do not use scissors, as you may accidentally cut and destroy the patch.

Figure #2



Removing the Liner

One side of the patch has the adhesive that attaches to your skin. The adhesive is covered by a protective liner that must be removed.

To separate the patch from the liner, hold the patch with the protective liner facing you. Peel off one side of the protective liner and discard it. Try to avoid touching the sticky side of the patch with your fingers.

Figure #3



Using the other half of the liner as a handle, apply the sticky side of the patch to a dry area of intact skin on the trunk of the body. Press the sticky side on the skin and smooth down.

Fold back the remaining side of the edge of the protective liner and pull it across the skin. Avoid touching the adhesive.

Figure #4



Don't worry if the patch buckles slightly because you can flatten it out after the liner has been removed. Apply the patch soon after opening the pouch and removing the liner.

Applying the Sandoz Estradiol Derm Patch

Apply the adhesive side to the spot you have chosen. Press it firmly in place with the palm of your hand for about 10 seconds, then run your finger around the edge, making sure there is good contact with the skin.

When and How to Remove the Patch

The Sandoz Estradiol Derm patch should be changed twice weekly. Always change it on the same 2 days of the week.

After you remove the patch fold it in half with the adhesive sides inwards. Throw it away, safely out of reach of children or pets.

Any adhesive left on your skin will rub off easily. Apply a new Sandoz Estradiol Derm 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 still does not stick, then apply a new patch and continue with 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 alternate 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 Sandoz Estradiol Derm 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 that you may do:

- choose the buttock as the site of application
- change the site of application of the Sandoz Estradiol Derm patch every time a new patch is applied, usually twice weekly.

Experience with the estradiol patch 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 Sandoz Estradiol Derm for you after a careful review of your medical needs. Use it only as directed and do not give it to anyone else.

If you have any questions, contact your doctor or pharmacist.

Overdose Symptoms

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

If more medication has been taken than what has been prescribed, remove the patch and contact either your doctor, hospital, or emergency department immediately.

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

Missed Dose

If you forget to change a patch at the scheduled time, apply a new patch as soon as you remember. No matter what day that happens, go back to changing the patch on the same day as your initial schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following effects have been reported in women taking estrogens (these include estrogens used for birth control).

- genital bleeding/spotting
- headache
- breast tenderness
- bloating
- weight gain

Check with your doctor as soon as possible if any of the following occur: swelling of the lower legs, ankles, fingers or abdomen due to fluid retention (oedema) persisting for more than 6 weeks, change in weight, change in your sex drive, easy bruising, excessive nose bleeds, painful and/or heavy periods (may be signs of growth of fibroids in the uterus) change in vaginal discharge (may be sign that too much estrogen is taken), vaginal thrush (vaginal fungal infection with severe itching, vaginal discharge), intolerable breast tenderness, persistent or severe skin irritation, itching under or around the patch, reddening of the skin after the patch has been removed, hair loss, excessive hairiness, spotty darkening of the skin, particularly on the face or abdomen (chloasma), rash, itching, acne,

dryness or discoloration of the skin, purple skin patches (purpura), headache, decline of memory or mental ability, uncontrollable jerky movements (chorea), contact lens discomfort, hearing loss, gall bladder disease (tendency to form gall stones).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Crushing chest pain or chest heaviness			✓
	Persistent sad mood			✓
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✓
	Migraine			✓
	Pain or swelling in the leg			✓
	Sudden partial or complete loss of vision			✓
	Sharp pain in the chest, coughing blood or sudden shortness of breath			✓
	Yellowing of the skin or eyes (jaundice)			✓
	Abdominal pain, nausea, or vomiting,		✓	
	Breast lump		✓	
	Unexpected vaginal bleeding, excessive heavy bleeding		✓	
	Increase in blood pressure		✓	

This is not a complete list of side effects. For any unexpected effects while taking Sandoz Estradiol Derm, contact your doctor or pharmacist.

HOW TO STORE IT

Sandoz Estradiol Derm should be stored between 15 and 30°C. Protect from freezing. **Do not store it out of the pouch.**

Sandoz Estradiol Derm patches should be kept out of reach of children and pets before and after use.

REPORTING SUSPECTED SIDE EFFECTS

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

Online: www.healthcanada.gc.ca/medeffect
 Toll-free phone: 1 866-234-2345
 Toll-free fax: 1 866-678-6789
 Postage Paid Mail: Canada Vigilance Program
 Health Canada
 AL 0701C
 Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document, plus the full Product Monograph prepared for health professionals, can be obtained by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062

or

by written request at:

145, Jules-Léger

Boucherville, (QC), Canada

J4B 7K8

or by e-mail at :

medinfo@sandoz.com

This leaflet was prepared by Sandoz Canada Inc.

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