PRESCRIBING INFORMATION

OGEN*

(estropipate)

Tablets 0.75 mg, 1.5 mg, 3.0 mg

Estrogen

Pfizer Canada Inc.
17,300 Trans-Canada Highway
Kirkland, Quebec, H9J 2M5

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OGEN*

estropipate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets / 0.75 mg, 1.5 mg, 3.0 mg	Lactose (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, under *other conditions).***

INDICATIONS AND CLINICAL USE

OGEN (estropipate, USP) is indicated for the treatment of menopausal and post-menopausal symptoms. OGEN should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

Pediatrics (<16 years of age): Safety and effectiveness of OGEN in paediatric patients have not been established (see **WARNINGS AND PRECAUTIONS, Special Populations**: **Pediatrics**).

CONTRAINDICATIONS

Estrogen & Estrogen/Progestin combinations are contraindicated in patients with any of the following disorders:

- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g. endometrial cancer).
- Known, suspected, or past history of breast cancer
- Endometrial hyperplasia.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy.
- Active or past history of arterial thomboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease).
- Classical migraine
- 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 due to ophthalmic vascular disease.
- 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 Prescribing Information.

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=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years. [21, 24, 27]

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. [21]

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.[27]

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.

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).[21]

The WHI study 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.[24]

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.[27]

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 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/carcinoma (if taken by women with intact uteri). OGEN 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. [21,22, 23] 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. [21, 27]

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). [21]

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. [27]

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. [22]

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. [23]

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.

Ear/Nose/Throat

Otosclerosis

Estrogens should be used with caution in patients with otosclerosis.

Endocrine and Metabolism

Glucose and lipid metabolism

A worsening of glucose tolerance and lipid metabolism has 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 hypertriglyceridemia need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Heme metabolism

Women with porphyria need special surveillance.

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).**

Other conditions

OGEN contains lactose. In patients with rare hereditary galactose intolerance, lactase deficiency or Glucose-galactose malabsorption, the severity of the condition should be taken into careful consideration before prescribing OGEN. The patients should be closely monitored.

Genitourinary

Vaginal Bleeding

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

Uterine leiomyomata

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.

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 postmenauposal 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. [21]

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. [27]

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/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 with or without progestins 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 diseases

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

Hepatic hemangioma

Particular caution is indicated in women with hepatic hemangiomas as estrogens 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. [25, 26]

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri 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). [25]

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]

Epilepsy

Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition. Treatment should be stopped if there is an increase in epileptic seizures.

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.

Special Populations

Nursing Women: Estrogen administration in lactating women has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of women receiving OGEN. The use of OGEN in lactating women is not recommended.

Pediatrics: Safety and effectiveness of OGEN in paediatric patients have not been established.

Monitoring and Laboratory Tests

Before OGEN (estropipate, USP) 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. 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 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 **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.

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; 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
Chloasma or melasma, which may persist when drug is discontinued; erythema multiform; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

Vascular disorders
Isolated cases of: thrombophlebitis; thromboembolic disorders.

CLINICAL TRIAL ADVERSE DRUG REACTIONS

No data are available.

Less Common Clinical Trial Adverse Drug Reactions:
No data are available.

Abnormal hematological and clinical chemistry findings
No data are available.

Post-Market Adverse Drug Reactions:
The following events have been reported in patients who have received OGEN: mouth ulceration, tongue ulceration, gait disturbance, hyperglycaemia, mobility decreased, cognitive disorder, convulsion, eating disorder, incontinence, dyspnoea and pruritus. It should be noted that the uncontrolled nature of post-marketing surveillance makes it difficult to determine definitively if a reported event was actually caused by OGEN, or to reliably assess causation in individual cases.

If adverse symptoms persist, the prescription of HRT should be re-considered.

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 published literature. It is unknown whether such interactions occur with drug products containing other forms of estrogens. Drug monitoring is recommended.

1. The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbital, phenytoin and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduce the plasma concentrations of ethinyl estradiol by 30 percent.

Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increase AUC values for ethinyl estradiol by 20 percent.

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

2. Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, these drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol).

Drug-Food Interactions

No Drug-Food interaction studies were conducted on OGEN. However, it is known that CYP3A4 inhibitors such as grapefruit juice may increase plasma concentrations of 17 β-estradiol and may result in side effects.

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 health care 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-Lifestyle Interactions

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

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 (T_4) as measured by column or radioimmunoassay; T3 resin uptake is decreased, reflecting the elevated TBG; free T_4 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 triglycerides and phospholipids 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

In general, estrogen should be given cyclically (21 to 25 days followed by a 5 to 7 day rest period) with progestogen in women with intact uteri in order to reduce endometrial hyperplasia/carcinoma. Withdrawal bleeding commonly occurs toward the end of the rest period. The addition of sufficient progestogen to promote conversion of the endometrium is mandatory in those patients who are receiving sufficient unopposed estrogen to cause vaginal bleeding or endometrial hyperplasia. Obviously, abnormal vaginal bleeding in such patients is an indication for prompt diagnostic measures.

Recommended Dose and Dosage Adjustment

As with most drugs, the dosage should be adjusted to the minimum required to control symptoms and the requirement for estrogen therapy should be reassessed periodically.

OGEN (estropipate, USP) is indicated for a variety of estrogen deficiency states. The usual daily dose is 0.75 mg to 3.0 mg estropipate (OGEN calculated as sodium estrone sulphate). Titrate dosage as necessary according to the individual patient's clinical response.

OGEN 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 a previous hysterectomy.

Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

Administration

OGEN (estropipate, USP) is administered orally.

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

Treatment
Give symptomatic treatment.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

OGEN (estropipate, USP) owes it therapeutic action to estrone, one of the three principal estrogenic steroid hormones of humans: estradiol, estrone and estriol. Estradiol is rapidly hydrolysed in the body to estrone, which in turn may be hydrated to the less active estriol. These transformations occur readily, mainly in the liver, where there is also free interconversion between estrone and estradiol.

Estrogens act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Pharmacodynamics
Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. They promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Along with other hormones such as progesterone, estrogens are intricately involved in the process of menstruation. Estrogens also affect the release of pituitary gonadotropins.

A depletion of endogenous estrogens occurs postmenopausally as a result of a decline in ovarian function, and may cause symptomatic vulvovaginal atrophy.

Pharmacokinetics

Absorption: Gastrointestinal absorption of orally administered estrogens is usually prompt and complete.

In a cross-over, randomized study of eight post-menopausal women aged 51-60, the pharmacokinetics of piperazine estrone sulphate 2.5 mg/day was compared to estradiol valerate 2.0 mg/day. Blood sampling was carried out on days 1 and 21. Levels of estrone (E_1), estradiol (E_2), estrone sulphate (E_1S), estradiol sulphate (E_2S) and estriol sulphate (E_3S) were measured by RIA. On average, the time required to obtain a maximum concentration of estrone (E_1), estradiol (E_2), estrone sulphate (E_1S), estradiol sulphate (E_2S) and estriol sulphate (E_3S) in the circulation is between 4.4 and 9.8 hours. Following a single dose of 2.5 mg piperazine estrone sulphate E_1, E_2 concentrations, measured by RIA, increase for approximately 6.4-9.8 hours to reach peak plasma concentrations of 1.3 and 0.25 nmol/L respectively.

Distribution: Estrone is 50-80% bound to protein as it circulates in the blood, usually as a conjugate with sulphate.

Metabolism: Inactivation of estrogens in the body occurs mainly in the liver. During cyclic passage through the liver, estrogens are degraded to less active estrogenic compounds and conjugated with sulphuric and glucuronic acids.

Excretion: In the normal menstrual cycle, the mean daily excretion of endogenous estrogens at the midovulatory maximum has been found to be 29 μg of estriol, 21 μg of estrone and 8 μg of estradiol (total, 58 μg). In normal women, after menopause, the average daily excretion of these three estrogens totals only 6 μg.

During the first 24 hours, 50% of estrone or estradiol is excreted via the kidney, 10% is found in the feces and the rest is reabsorbed.

The plasma elimination half-lives of estrone (E_1), estradiol (E_2) and estrone sulphate (E_1S) are 18.5, 34.7, 11.8 hours respectively.

Estrogen Pharmacology

OGEN (estropipate, USP) is a natural estrogenic substance prepared from purified crystalline estrone, solubilized as the sulphate and stabilized with piperazine. It is appreciably soluble in water and has almost no odour or taste. The amount of piperazine in OGEN is not sufficient to exert a pharmacological action. Its addition ensures solubility, stability and uniform potency of the estrone sulphate.

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

In premenopausal women, the ratio of estradiol-17β (E_2) to estrone (E_1) (i .e. E_2/ E_1 ratio) in the plasma is in the range of 0.5 to 2, depending on the phase of the menstrual cycle. The E_2/ E_1 ratio for untreated postmenopausal women is below 0.5.
Loss of the ovarian estradiol-17β 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, resulting in osteoporosis; alterations in lipid metabolism; urogenital atrophy, causing dyspareunia and urinary incontinence.
The protection against endometrial hyperplasia 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 at controlled room temperature, 15-30 º C.

SPECIAL HANDLING INSTRUCTIONS
Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING
OGEN (estropipate, USP) Tablets are available as:

- OGEN (0.75 mg estropipate, calculated as sodium estrone sulphate 0.625 mg), yellow-coloured oval tablet, scored, embossed with "U" and "3772" on left and right halves, supplied in bottles of 100.

- OGEN (1.5 mg estropipate, calculated as sodium estrone sulphate 1.25 mg), peach-coloured oval tablet, scored, embossed with "U" and "3773" on left and right halves, supplied in blisters of 20 in cartons of 5 blisters and in bottles of 100.

- OGEN (3.0 mg estropipate, calculated as sodium estrone sulphate 2.5 mg), blue-coloured oval tablet, scored, embossed with "U" and "3774" on left and right halves, supplied in blisters of 20 in cartons of 5 blisters and in bottles of 100.

Composition:
Each OGEN (estropipate, USP) tablet contains an active ingredient, estropipate USP, 0.75 mg, 1.5 mg or 3.0 mg.

The inactive ingredients include: lactose monohydrate and/or lactose anhydrous, magnesium stearate, potassium phosphate dibasic, tromethamine, hydroxypropyl cellulose, sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, hydrogenated vegetable oil wax, purified water, alcohol.
OGEN 0.75 mg also contains: FD&C Yellow No. 10 and FD&C Yellow No. 6.
OGEN 1.5 mg also contains: FD&C Yellow No. 6.
OGEN 3.0 mg also contains: FD&C Blue No. 2.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

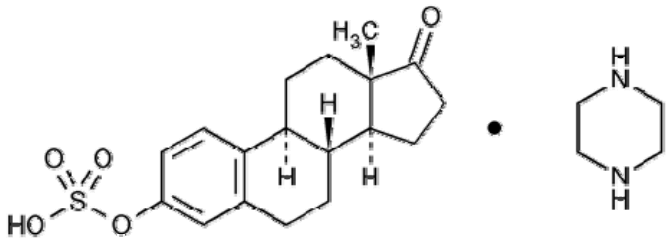
Drug Substance

Proper name: estropipate

Chemical name: estra-1,3,5(10)-trien-17-one,3-(sulfooxy)-, compound with piperazine (1:1).

Molecular formula and molecular mass: $C_{18}H_{22}O_5S \cdot C_4H_{10}N_2$, 436.57

Structural formula:



Physicochemical properties:

Physical form: white to yellowish white, fine crystalline powder
Solubility: very slightly soluble in water and in alcohol.

Melting Point: 190°C

CLINICAL TRIALS

Study demographics and trial design

The following studies discussed are based on published literature.

A double-blind, crossover study in 168 symptomatic women (131/168 completers) with mean age of 49 years (range 31-78 years) compared 3.0 mg estropipate versus 1.25 mg conjugated estrogen equine (CEE) for the treatment of menopausal symptoms. Specifically, when treated with either estropipate or CEE for the first 21 day cycle, followed by treatment cross-over to the second 21 day cycle, the effect of both treatments in rendering asymptomatic or considerable improvements in the menopausal symptoms examined was established. No flushes and sweats were reported by 45% and 56% of the patients, respectively, during either cycle treatment. Similar results were obtained for symptoms of headaches (46%), insomnia (53%), depression (47%), and anxiety (38%). Thirty five of the 131 patients reported side-effects during their estropipate treatment. Common side-effects reported were breast tenderness, nausea, edema and weight gain and lack of energy.

A double-blind, crossover study involving 40 menopausal women between the ages of 38 and 46 years (40/40 completers) compared clinical efficacy of estropipate and ethinyl oestradiol for the treatment of menopausal symptoms. Placebo was administered for the first 21 days followed by a 7 day treatment-free period. Twenty patients received a daily dose of 3.0 mg estropipate and 20 patients received 0.03 mg of ethinyl oestradiol, each for 21 consecutive days with a 7 day treatment-free interval between treatment crossovers. Absence of flushes was reported by 50% of patients, and 52.5% reported no sweats during active therapy. A greater percentage of patients reported that flushes and sweats were significantly less severe during estropipate therapy ($p<0.05$). Insomnia, depression and anxiety were significantly relieved ($p<0.05$) to the same extent by both treatments ($p>0.05$).

An 8-week placebo-controlled, randomized clinical trial was conducted in 20 symptomatic women between the ages of 35 and 45 years for the treatment of menopausal symptoms. Patients were randomized to either placebo or 3.0 mg/daily estropipate. Weekly follow-ups were undertaken to enquire into symptom relief and plasma estradiol levels were taken as a measure of treatment success. All patients receiving estropipate experienced plasma estradiol level increase and associated relief of symptoms. The control group showed neither elevation of plasma estradiol nor relief of symptoms.

DETAILED PHARMACOLOGY

See **Action and Clinical Pharmacology (Part I)**.

TOXICOLOGY

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

OGEN*
(estropipate)
Tablets 0.75mg, 1.5 mg, and 3.0 mg

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

ABOUT THIS MEDICATION

What the medication is used for:
OGEN is used to treat menopausal or and postmenopausal symptoms.

OGEN 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:
OGEN is a medicine that contains a manufactured estrogen hormone that is similar to the estrogen produced by a woman's ovaries. **OGEN** alleviates symptoms associated with menopause.

When it should not be used:
You should not take estrogen if you have or have had any of the following conditions:

- Certain cancers including cancer of the breast, cancer of uterus or of the endometrium (lining of the uterus)
- Endometrial hyperplasia (overgrowth of the uterus lining)
- If you have active thrombophlebitis (inflamed varicose veins) or you currently have a problem with abnormal blood clots forming in your blood vessels, or have ever had such a problem in the past. This may cause painful inflammation of the veins (thrombophlebitis) or blockage of a blood vessel in the legs (deep vein thrombosis), lungs (pulmonary embolism) or other organs.
- Stroke or heart attack
- Migraine headaches
- Heart disease
- Liver disease
- Unusual genital bleeding
- Pregnancy
- Partial or complete loss of vision due to disease of the blood vessels in the eye
- Known or suspected allergy to **OGEN** or to any of its ingredients

What the medicinal ingredient is:
estropipate.

What the nonmedicinal ingredients are:
alcohol, colloidal silicon dioxide, FD&C Yellow No. 10, FD&C Yellow No. 6 and FD&C Blue No. 2, hydrogenated vegetable oil wax, hydroxypropyl cellulose, lactose monohydrate and/or lactose anhydrous, magnesium stearate, microcrystalline cellulose, potassium phosphate dibasic, purified water, sodium starch glycolate, tromethamine.
OGEN 0 .75 mg also contains: FD&C Yellow No. 10 and FD&C Yellow No. 6. **OGEN** 1.5 mg also contains: FD&C Yellow No. 6. **OGEN** 3.0 mg also contains: FD&C Blue No. 2.

What dosage forms it comes in:
OGEN 0.75 mg (0 .75 mg estropipate, calculated as sodium estrone sulphate 0 .625 mg) is supplied as a yellow-coloured, oval tablet.
OGEN 1.5 mg (1.5 mg estropipate, calculated as sodium estrone sulphate 1.25 mg) is supplied as a peach-coloured, oval tablet.
OGEN 3.0 mg (3.0 mg estropipate, calculated as sodium estrone sulphate 2.5 mg) is supplied as a blue-coloured, oval tablet.
Each **OGEN** tablet contains 0.75 mg, 1.5 mg or 3.0 mg estropipate.

WARNINGS AND PRECAUTIONS

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

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 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 HRT.

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

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

Overgrowth of the lining of the uterus and cancer of the uterus The use of estrogen-alone therapy by post menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

If you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month to reduce the risk of endometrial hyperplasia.

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

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma.

Progestin therapy is therefore not 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 post-menopausal 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 post-menopausal 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 post-menopausal 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 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 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 post-menopausal women age 65 and over with prior hysterectomy taking oral estrogen-alone compared to women taking placebo.

BEFORE you use OGEN 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 uterine fibroids or endometriosis
• have a history of liver disease, liver tumours or jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
• 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
• 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 been diagnosed with porphyria (a disease of blood pigment)
• have a history of high cholesterol or high triglycerides
• are pregnant or may be pregnant
• have had a hysterectomy (surgical removal of the uterus)
• smoke

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products (such as St-John's wort). Some medications (such as medications for high blood pressure, diabetes, blood clots, sleeping, anxiety, seizures, pain-relief and tuberculosis) may affect how **OGEN** works. **OGEN** may also affect how other medicines work.

PROPER USE OF THIS MEDICATION

Usual dose:
- Take **OGEN** as directed by your doctor or pharmacist.
- Swallow the tablet whole, with some water.
- You and your doctor should discuss regularly, about every 3 to 6 months, whether you still need to take **OGEN** for your symptoms.
- The usual daily dose of **OGEN** is 0.75 mg to 3.0 mg estropipate. The dose of **OGEN** should be adjusted by your doctor depending on how well it works for you.

Missed dose:
Do not take a double dose to make up for a forgotten tablet. It is important that you take OGEN regularly at the same time each day. If you forget to take a dose, take it as soon as you remember, as long as it is within a few hours of the missed dose. If it is longer than that since the missed dose, or if you do not remember whether you took a dose or not, then skip that dose, and wait to take the next dose at the correct time.

Overdose:
Overdose with estrogen may cause nausea, breast discomfort, fluid retention bloating or vaginal bleeding in women. In case of overdose, call your doctor, hospital or poison control center immediately.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with most drugs, **OGEN** can cause some side effects.

The most common side effects are irregular vaginal spotting, headache, breast pain, water retention, bloating, stomach/abdominal cramps, bloating, changes in appetite, body weight, and libido.

Other side effects are high blood pressure, liver problems, high blood sugar, fluid retention, enlargement of benign tumours in the uterus (fibroids), irritability, vaginal yeast infections, acne, spotty darkening of the skin and hair loss.

If you notice any side effects not mentioned above, or any of the above-mentioned side effects persist or become bothersome, please contact your doctor or pharmacist.

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	
Abdominal pain, nausea or vomiting		√	
Breast lump		√	

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

	Talk with your doctor or pharmacist		
Crushing chest pain or chest heaviness			√
Pain or swelling in the leg			√
Persistent sad mood			√
Sharp pain in the chest, coughing blood or sudden shortness of breath			√
Sudden partial or complete loss of vision			√
Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			√
Unexpected vaginal bleeding		√	
Yellowing of the skin or eyes (jaundice)			√

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

HOW TO STORE IT

- Store between 15°C and 30°C, in the original package. Do not freeze.
- Always keep **OGEN** out of reach and sight of children.

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 Ca nada Vigilance:
Online: www.healthcanada.gc.ca/medeffect
Toll-free phone: 1-866-234-2345
Toll-free fax: 1-866-1578-6789
Postage Paid Mail: Canada Vigilance Program
Health Canada
AL 0701C
Ottawa, Ontario K1A OK9
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 prescribing information, prepared for health professionals can be found at:
http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001.

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