PRODUCT MONOGRAPH

[Pr]ESTRAGYN® VAGINAL CREAM

Estrone vaginal cream

containing estrone 0.1% w/w

ESTROGEN

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TABLE OF CONTENTS

ESTRAGYN® Vaginal Cream

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedical Ingredients
Intravaginally	0.1%w/w Estrone Vaginal cream	Mineral oil, methyl paraben, propyl paraben. For a complete listing see Dosage Forms, Composition and Packaging Section.

INDICATIONS AND CLINICAL USE

Estragyn Vaginal Cream is indicated for the *treatment of the symptoms of vulvovaginal atrophy due to estrogen deficiency.*

Estragyn Vaginal Cream should be prescribed with an appropriate dosage of a progestin for women with intact uteri to prevent endometrial hyperplasia/carcinoma.

Estragyn Vaginal Cream is intended for short term use.

Geriatrics (>65 years of age): See above indications

Pediatrics (<16 years of age): Estragyn Vaginal Cream is not indicated for use in children.

CONTRAINDICATIONS

Estragyn Vaginal Cream should not be administrated to patients with any of the following conditions:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- 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)
- 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 vein thrombosis or pulmonary embolism) or active thrombophlebitis.
- Partial or complete loss of vision due to ophthalmic vascular disease
- Classical migraine
- Breastfeeding
- The mineral oil found in Estragyn Vaginal Cream is not compatible with the latex rubber found in most condoms.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions Box

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.[1 2 3]

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.[1]

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. [2]

Therefore, the following should be given 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).[1]

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 one year and persisted in each year thereafter.[3]

In the *estrogen–alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.[2]

It is recommended that estrogens with or without progestins 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 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 be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

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

Endometrial Hyperplasia & Endometrial Carcinoma

Estragyn Vaginal Cream, an 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.

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.[8,9]

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.[1,4,5] 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.[1,2]

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).[1]

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

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- No statistically significant difference in the rate of CHD.[2]

HERS and HERS II findings

In the Heart and Estrogen/progestin Replacement Studies (HERS) of postmenopausal women with documented heart disease (n=2,763,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 years.[4] From the original HERS trial, 2,321 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.[5]

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

Heme metabolism

Women with porphyria need special surveillance.

Calcium and phosphorous metabolism

Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hyperglycaemia and 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 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.[1]

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.[2]

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>30kg/m²) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given 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 replacement 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 the 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.[6,7]

In the *estrogen plus progestin* arm of the WHIMS (n=4,532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5mg 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).[6]

In the *estrogen-alone* arm of the WHIMS (n=2,947), 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.[7]

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).[7]

Epilepsy

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

Renal

Fluid retention

Estrogens with or without progestins 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

Pregnant Women: Estragyn Vaginal Cream should not be used during pregnancy (please see CONTRAINDICATIONS).

Nursing Women: Estragyn Vaginal Cream should not be used during lactation (please see CONTRAINDICATIONS).

Pediatrics (<16 years of age): Estragyn Vaginal Cream is not indicated for use in children.

Monitoring and laboratory Tests

Before Estragyn Vaginal Cream 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 multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

Vascular disorders

Isolated cases of: thrombophlebitis; thromboembolic disorders.

Clinical Trial Adverse Drug Reactions

Data are not available.

Less Common Clinical Trial Adverse Drug Reactions

Data are not available.

Post-Market Adverse Drug Reactions

Case #1- Complaint of a burning sensation.

Case# 2- Complaint of inflammation and vaginal discharge.

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

Potential Drug-Drug Interactions Summary as Associated With Estrogen Therapy

Proper Name or Drug Classes	Reference	Effect	Clinical Comment
Oral antidiabetic drugs	The Essential Guide to Prescription Drugs 2002 Author: James J. Rybacki, Pharm. D.	May cause loss of glucose control and high blood sugars.	Caution is warranted and therapeutic concentration monitoring is recommended
Warfarin		May cause alterations of prothrombin activity.	
Rifampin		May decrease the effects of estrogens	
Anticonvulsants:	The Essential Guide to	May decrease the	Caution is warranted and therapeutic

Proper Name or Drug Classes	Reference	Effect	Clinical Comment
Barbiturates (Phenobarbital) Phenytoin Carbamazepine Primidone	Prescription Drugs 2002 Author: James J. Rybacki, Pharm. D.	effects of estrogens	concentration monitoring is recommended
Corticosteroids	Fiche professionnelle Santexpert	May increase the effects of Corticosteroids	
Ascorbic acid	Health Canada Branch	May increase AUC and /or plasma concentrations of ethinyl estradiol	
Acetaminophen		May increase AUC and /or plasma concentrations of ethinyl estradiol	
Atorvastatin (Lipitor)	The Essential Guide to Prescription Drugs 2002 Author: James J. Rybacki, Pharm. D.	May increase AUC for ethinyl estradiol by as much as 20%	
Cyclosporine	Health Canada Branch	Ethinyl estradiol may cause increased plasma concentrations of cyclosporine	
Prednisolone		Ethinyl estradiol may cause increased plasma concentrations of prednisolone.	
Theophylline		Ethinyl estradiol may cause increased plasma concentrations of theophylline.	
Troglitazone		Co-administrated with certain ethinyl estradiol drug (e.g. oral contraceptives) may	

Proper Name or Drug Classes	Reference	Effect	Clinical Comment
		reduce plasma concentrations of estradiol by as much as 30%	
Salicylic acid		May increase clearance of salicylic acid.	
Temazapam		May increase clearance of temazapam	
Morphine	Health Canada Branch	May increase clearance of morphine	
Clofibric acid		May increase clearance of Clofibric acid	

Drug-Food Interactions

As other inhibitors of CYP3A4, grapefruit juice may increase plasma concentrations of estrogens, possibly resulting 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-Laboratory Test Interactions

The results of certain endocrine and liver function test 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; T_3 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 hormone replacement therapy (HRT) 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**

The treatment is initiated by the patient at a time of day convenient to the patient. Repeat dosages should coincide with this chosen schedule.

Estragyn Vaginal Cream should be prescribed with an appropriate dosage of a progestin for women with intact uteri to prevent endometrial hyperplasia/carcinoma.

- **Recommended Dose and Dosage Adjustment**

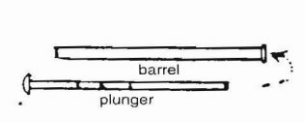
Patients should be started at the lowest dose.

The recommended dose is 0.5 to 4 grams per day taken intravaginally, adjusted to the lowest amount that controls symptoms. Estragyn Vaginal Cream is intended for short term use. Administration should be cyclic (e.g., three weeks on one week off).

- **Missed Dose**

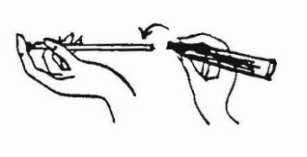
If a dose has been clearly missed it is safer to restart at the time of the next dose. Do not double dose.

- **Administration**

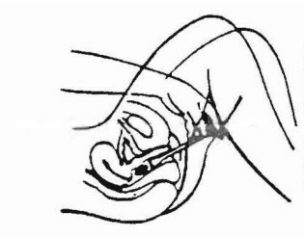


Estragyn Vaginal Cream is administered with the use of the supplied vaginal applicator, which consists of a calibrated plunger and a barrel. The applicator is calibrated in half gram increments to measure and deliver 0.5 to 4 grams of cream.

Instructions for the proper use of the supplied vaginal applicator: Before piercing the tube, screw the applicator barrel to the tube. Repeat this at least twice to ensure that the applicator screws on with ease.



Fill the applicator by proceeding as follows: use the inversed cap to pierce the tube seal. Screw the applicator barrel firmly to the tube with the plunger fully in. Squeeze the tube to fill cream into the barrel. Measure the required amount of cream by aligning the line calibrator on the plunger to the barrel end.



Inserting the vaginal applicator with cream: patients should be lying on their back. Using either hand, grasp the barrel of the applicator firmly with thumb and middle finger. Do not push the plunger with the index finger until after the applicator is in the proper position in the vagina. Pointing the applicator slightly downward, insert it deeply into the vagina as far as it will comfortably go without using force. Now, push the plunger all the way down to deposit the cream in the vagina. Withdraw the applicator from the vagina when the cream has been deposited.

Care of the applicator: Separate the plunger from the barrel by pulling it all the way out. Wash both sections of the applicator thoroughly with mild detergent and warm water, allowing the water to flow through the barrel to rinse well. Sterilisation of the applicator is not necessary and extremely hot water should not be used because it may soften the plastic applicator. Dry the applicator and store it in a clean place.

Caution: the applicator should be used only on the advice of a physician.

Estragyn Vaginal Cream 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.

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

Symptomatic treatment should be given.

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

ACTION AND CLINICAL PHARMACOLOGY

- **Mechanism of Action**

  Estrogen drug products act by regulating the transcription of a limited number of genes. They may act directly at the cell's surface via a non "estrogen receptor" mechanism or directly with the estrogen receptor inside the cell. 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 the wall of blood vessels, 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

  Estrone is water soluble and can be readily absorbed into the blood stream through skin and mucous membranes.

  Distribution

  The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are distributed in the body and generally found in higher concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Absorbed hormone is metabolized by the liver much the same as endogenous hormone. Complex metabolic processes create a dynamic equilibrium of inter conversion between estrone and estradiol and between esterified and non esterified forms.

Estrogen administered intravaginally is not subject to true "first-pass" metabolism, but will undergo hepatic uptake, metabolism, and enterohepatic recycling. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; but, they are re-absorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favour excretion through the kidneys since tubular re-absorption is minimal.

Excretion

A portion of the estrogen is excreted into the bile to be reabsorbed via the intestine and back to the liver. During the course of enterohepatic recirculation, estrogens are desulfated and resulfated, undergo degradation to less active estrogens such as estriol, are oxidized to nonestrogenic substances which interact with catecholamine metabolism and are conjugated with glucuronic acids to be excreted in the urine.

- **Special Populations and Conditions**

  No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Estrogen pharmacology

There are 3 main estrogens found in the human body they being 17β-estradiol, estrone and estriol. Estradiol the most potent is produced by the ovarian follicle during child bearing years. However at menopause most estrogen is derived from the conversion of androstenedione to estrone by peripheral tissues. In the case for estrone in a vaginal cream the estrogen is present to bind to the receptors of estrogen responsive tissue that line the vagina.

Although the amount of estrone available per treatment is low, the concomitant use of a progestin is a necessary precaution to protect against endometrial hyperplasia in women with intact uteri.

STORAGE AND STABILITY

Store at room temperature between 15°C and 30°C. Avoid freezing as it may cause the cream to separate destroying its properties.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Estragyn Vaginal Cream is a vaginal cream containing 0.1% estrone. If used continuously then lower the dosage to the lowest amount that controls the symptoms. Estragyn Vaginal Cream comes only in 0.1% w/w concentration of estrone.

Non medicinal ingredients are as follows: arlacel 165, isopropyl myristate, methyl paraben, mineral oil, Peg 40 stearate, propyl paraben, sorbitan monostearate, stearic acid, water.

Estragyn Vaginal Cream is available as 20g and 45g size tubes and comes complete with 0 to 4 gram applicator calibrated in 0.5g increments. Included in the boxed package are the detailed applicator instructions on its use and its hygienic maintenance.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name: Estrone

Chemical name:

Estra-1,3,5(10)-trien-17-one,3-hydroxy-3-hydroxyestra-1,3,5(10)-trien-17-one [53-16-7]

Molecular formula: $C_{18}H_{22}O_2$

Molecular mass: 270.366 g/mol

Structural formula:

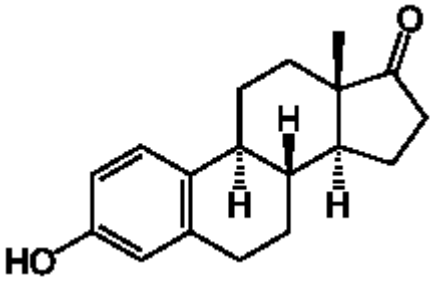


Figure 1 - Estrone

PIVOTAL CLINICAL TRIALS

Efficacy and Safety Studies

There have been no pivotal clinical trials specific to the use of Estragyn Vaginal Cream. Moreover there is not an abundance of published studies on the use of intra vaginal estrogen therapy. The estrogens currently available are of a diverse range which includes conjugated estrogens, 17 beta-estradiol, and estrone. Also they vary in the delivery systems used: vaginal creams versus vaginal tablets versus vaginal rings. However common characteristic of these low dose vaginal applied hormones is that they effectively alleviate the symptoms of vaginal atrophy. Early investigation shows cytological and subjective improvement after low dose intra vaginal treatment over relatively short periods of time.[10,11,12] Again this assessment is reflected in the Cochrane Collaboration: Local estrogen for vaginal atrophy in postmenopausal women (Review).[13] On a subjective evaluation there were differences noted between groups receiving estrogens as compared to a non-estrogenic moisturizer. However there were no significant differences between estrogen receiving groups for assessment of atrophy, pallor, petechaie, friability, and dryness. In cytological assessment there were no significant differences between groups for karyopknotic index, maturation value and vaginal health index. In terms of safety there were no significant differences between

groups for outcomes of hyperplasia, proliferation of the endometrium or endometrial thickness. As a cautionary statement and also pointed out by the authors any interpretation has to consider that the review was based on combined results of many separate trials with: trial variation, small trial numbers and significant variance in results. Also these studies do not look at long term effects of treatment and therefore the full term treatment should not be extended without consideration of closer monitoring.[13]

It is also well known and demonstrated that intra-vaginal applied hormones are absorbed systemically. In light of the findings of the WHO on HRT a concern was raised on the estrogenic link to breast cancer. However that study did not include vaginal applications of low dose estrogens. Published data by Dew J.E. et al did not appear to associate topical vaginal estrogen therapy with an increased risk of breast cancer however that study was too small in numbers to be conclusive[14]. Kendall et al in the Annals of Oncology January 2006 was able to demonstrate raised systemic estradiol levels in patients having taken low dose vaginal tablets. These patients were in a high risk category and taking an adjuvant aromatase inhibitors and concludes that this treatment is contraindicated in this group of patients[15]. Until greater assurance is available, persons at higher risk should not be candidates for intra-vaginal estrogen therapy.

DETAILED PHARMACOLOGY

See **Actions and Clinical Pharmacology** section under 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

[Pr]ESTRAGYN® VAGINAL CREAM
(Estrone, 0.1% w/w)

IMPORTANT: PLEASE READ

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

ABOUT THIS MEDICATION

What the medication is used for:

Estragyn Vaginal Cream is used to treat the:
- dryness
- itching and
- burning

in and around the vagina due to a lack of estrogen.

Estragyn Vaginal Cream should not be used by women with intact uteri unless it is prescribed in association with a progestin. Estragyn Vaginal Cream is intended for short term use.

Estragyn Vaginal Cream 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

Estrone which is the active component of Estragyn Vaginal Cream contributes to the growth of the epithelial cells of the vaginal walls to improve their thickness and elasticity, to aid in lubrication and provide relief from itching and dryness. The treatment is working when there is relief from the symptoms of vaginal dryness and itching.

When Estragyn Vaginal Cream should not be used:

Before using Estragyn Vaginal Cream be sure to tell your doctor if you have any of the following problems, as Estragyn Vaginal Cream should not be used under these conditions:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a listing see "**What the medical ingredient is**" and "**What the nonmedicinal ingredients are**".
- Liver dysfunction (serious liver disease) or disease as long as liver function tests have failed to return to normal.
- If you currently have or have ever had cancer of the uterus or endometrium (lining of the womb) or any other estrogen-dependent cancer.
- Endometrial hyperplasia (overgrowth of the lining of the uterus).
- 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, heart attack, coronary heart disease.)
- Active or past history of problems with blood clots forming in the blood vessels including in the legs (deep vein thrombosis), lungs (pulmonary embolism) or other organs.
- Thrombophlebitis (painful inflammation of the veins in the legs)
- Partial or complete loss of vision due to blood vessel disease of the eye (ophthalmic vascular disease).
- If you are breastfeeding.
- If you have to use latex condoms for any reason
- If you experience migraine headaches

What the medicinal ingredient is:

Estrone

What the nonmedicinal ingredients are:

Arlacel 165, isopropyl myristate, methyl paraben, mineral oil, Peg 40 stearate, propyl paraben, sorbitan monostearate, stearic acid, water.

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 progestin should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestin 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 WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

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

Estrogens with or without progestin 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 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 your uterus removed, you are not at risk of 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 post-menopausal 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 Estragyn Vaginal Cream 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 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 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
- If you use latex condoms for any reason, as they are not compatible with the mineral oil found in Estragyn Vaginal Cream.
- 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
- If you are breastfeeding

INTERACTIONS WITH THIS MEDICATION

Drug interactions

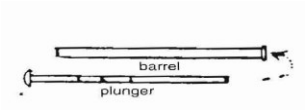
Some medications (such as medications for high blood pressure, diabetes, blood clots, sleeping, anxiety, seizures, pain-relief and tuberculosis) may affect how Estragyn Vaginal Cream works. Estragyn Vaginal Cream may also affect how other medicines work.

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).

PROPER USE OF THIS MEDICATION

Usual dose

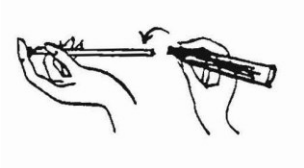
The dosage is 0.5 – 4 g daily used intravaginally. Use cyclically 3 weeks on 1 week off and then discontinue treatment as soon as possible. If used continuously then lower the dosage to the lowest amount that controls symptoms. You and your healthcare provider should talk regularly about whether the current dose of Estragyn Vaginal Cream helps relieve your symptoms and whether you still need treatment with Estragyn Vaginal Cream. Use according to your doctor's instructions. Estragyn Vaginal Cream is intended for short-term use.



The plastic applicator provided with this package is specifically designed to permit proper administration of a measured amount of vaginal cream. The applicator consists of a calibrated plunger and a barrel.

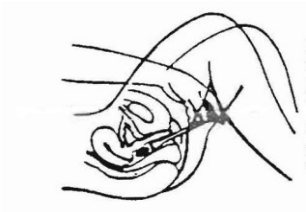
Instructions for the proper use of the supplied vaginal applicator:

- Before piercing the tube, screw the applicator barrel to the tube. Repeat this at least twice to ensure that the applicator screws on with ease. If the applicator does not screw to the tube, please contact Searchlight Pharma Inc. at 1-855-331-0830.



Fill the applicator by proceeding as follows:

- Remove the cap from the tube.
- Pierce the tube end with the pointed end of the cap
- Screw the applicator barrel firmly to the tube with the plunger fully in.
- Squeeze the tube to fill the applicator with the prescribed dose.
- Measure the required amount of cream by aligning the line calibrator on the plunger to the barrel end.



Inserting the vaginal applicator with cream:

- Lie on your back.
- Using either hand, grasp the barrel of the applicator firmly with thumb and middle finger.
- Pointing the applicator slightly downward, insert it deeply into the vagina as far as it will comfortably go without using force.
- Do not push the plunger with the index finger until after the applicator is in the proper position in the vagina.
- Push the plunger all the way down to deposit the cream in the vagina.
- Gently remove the applicator from the vagina.

Care of the applicator:

- Separate the plunger from the barrel by pulling it all the way out.
- Wash both sections of the applicator thoroughly with mild detergent and warm water, allowing the water to flow through the barrel to rinse well.
- Sterilisation of the applicator is not necessary and extremely hot water should not be used because it may soften the plastic applicator.
- Dry the applicator and store it in a clean place.

Caution: the applicator should be used only on the advice of a physician.

Overdose

Excessive amounts of estrogen may cause nausea, abdominal cramps, headaches, and dizziness or a feeling of general indisposition.

In case of a suspected overdose, contact a health care practitioner, hospital emergency department or regional poison control center immediately.

Missed Dose

If a dose has been clearly missed it is safer to restart at the time of the next dose. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Self Limiting Side Effects Include:

Spotting, changes in vaginal secretion have been associated with estrogen vaginal cream. Discontinue use and speak to your doctor if the condition persists beyond a few days.

The following table consists of serious side effects associated with hormone replacement therapies in general. If any conditions arise where cessation is indicated below then do so.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency (common or uncommon)	Symptom/possible side 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		✔	
	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 Estragyn Vaginal Cream, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature between 15°C and 30°C. Avoid freezing as it may cause the cream to separate destroying its properties.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

Reporting Side Effects

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

3 ways to report:

- Online at MedEffect; (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php)
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect. (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php)

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

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be obtained by calling Searchlight Pharma Inc. at 1-855-331-0830

This leaflet was prepared by Searchlight Pharma Inc.

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