ESTRADIOL- estradiol gel 0.1% gel
Xiromed, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ESTRADIOL GEL 0.1% safely and effectively. See full prescribing information for ESTRADIOL GEL 0.1%.

ESTRADIOL GEL, for topical use

Initial U.S. Approval: 1975

WARNING: ENDOMETRIAL CANCER

WITH UNOPPOSED ESTROGEN IN WOMEN WITH A UTERUS

See full prescribing information for complete boxed warning.
There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)

RECENT MAJOR CHANGES

Boxed Warning, Cardiovascular Disorders, Breast Cancer, Probable Dementia	removed 2/2026
Dosage and Administration, Important Use Information (2.1)	2/2026
Contraindications (4)	2/2026
Warnings and Precautions, Cardiovascular Disorders (5.1)	2/2026
Warnings and Precautions, Malignant Neoplasms (5.2)	2/2026
Warnings and Precautions, Risks Associated with Co-administration of Estrogen Plus Progestogen (5.3)	2/2026
Warnings and Precautions, Probable Dementia	removed 2/2026
Warnings and Precautions, Addition of a Progestogen When a Woman Has Not Had a Hysterectomy	removed 2/2026

INDICATIONS AND USAGE

Estradiol gel 0.1% is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause (1.1).

DOSAGE AND ADMINISTRATION

Daily administration of 0.25 to 1.25 grams of estradiol gel 0.1% to the right or left upper thigh on alternating days. Women should be started with the lowest effective dose and the dose should be evaluated periodically (2).

DOSAGE FORMS AND STRENGTHS

Single-dose 0.25, 0.5, 0.75, 1.0, and 1.25 gram-filled foil packets containing 0.25, 0.5, 0.75, 1.0, and 1.25 mg estradiol, respectively (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Breast cancer or a history of breast cancer (4, 5.2)
- Estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (e.g., stroke and MI), or history of these conditions (4, 5.1)
- Known anaphylactic reaction, angioedema, or hypersensitivity to estradiol gel 0.1% (4)
- Hepatic impairment or disease (4, 5.9)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

- Cardiovascular Disorders: Increased risk of PE, DVT, and stroke with estrogen-alone therapy. Discontinue if an arterial or venous thrombotic or thromboembolic event occurs. (5.1)
- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.8, 5.9)
- Monitor thyroid function in women on thyroid replacement therapy (5.10, 5.21)

ADVERSE REACTIONS

The most common adverse reactions (incidence >5 percent and greater than placebo) in any estradiol gel 0.1% treatment group are metrorrhagia, breast tenderness, vaginal mycosis, nasopharyngitis, and upper respiratory tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Xiromed, LLC. at 844-XIROMED (844-947-6633) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER WITH UNOPPOSED ESTROGEN IN WOMEN WITH A UTERUS

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestogen to estrogen-only therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.**
- **Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in menopausal women abnormal genital bleeding of unknown etiology *[see Warnings and Precautions (5.2)].***

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

The timing of estradiol gel 0.1% initiation can affect the overall benefit-risk profile. Consider initiating estradiol gel 0.1% in women <60 years old or <10 years since menopause onset *[see Warnings and Precautions (5), Use in Specific Populations (8.5) and Clinical Studies (14)].*

When estrogen is prescribed for a menopausal woman with a uterus, the addition of a progestogen has been shown to reduce the risk of endometrial cancer. There are possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens. See prescribing information for progestogens indicated for the prevention of endometrial hyperplasia in non-hysterectomized menopausal women receiving estrogens *[see Warnings and Precautions (5.2, 5.3)]*.

Generally, a woman without a uterus, does not need to use a progestogen with estrogen therapy. In some cases, however, hysterectomized women with a history of endometriosis may benefit from the addition of a progestogen *[see Warnings and Precautions (5.13)].*

2.2 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Start therapy with the 0.25 grams applied once daily on the skin of either the right or left upper thigh. Adjust the dose up to a maximum of 1.25 grams, as needed.

The application surface area should be about 5 by 7 inches (approximately the size of two palm prints). The entire contents of a unit dose packet should be applied each day. To avoid potential skin irritation, apply estradiol gel 0.1% to the right or left upper thigh on alternating days. Do not apply Estradiol gel 0.1% on the face, breasts, or irritated skin or in or around the vagina. Allow gel to dry after application before dressing. Do not wash the application site within 1 hour after applying estradiol gel 0.1%. Avoid contact of the gel with eyes. Wash hands after application.

3 DOSAGE FORMS AND STRENGTHS

Estradiol gel 0.1% is available in five doses of 0.25, 0.5, 0.75, 1.0, and 1.25 grams for transdermal application (corresponding to 0.25, 0.5, 0.75, 1.0, and 1.25 mg estradiol, respectively). Estradiol gel 0.1% is a clear, colorless gel, which is odorless when dry.

4 CONTRAINDICATIONS

Estradiol gel 0.1% is contraindicated in women with any of the following conditions:

- Abnormal genital bleeding of unknown etiology *[see Warning and Precautions (5.2)]*
- Current or history of breast cancer *[see Warning and Precautions (5.2)]*
- Estrogen-dependent neoplasia *[see Warning and Precautions (5.2)]*
- Active DVT, PE, or history of these conditions *[see Warning and Precautions (5.1)]*
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these conditions *[see Warning and Precautions (5.1)]*
- Known anaphylactic reaction, angioedema, or hypersensitivity to estradiol gel 0.1%

- Hepatic impairment or disease *[see Warnings and Precautions (5.9)]*
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

Estradiol gel 0.1% is contraindicated in women with active DVT, PE, stroke, or a history of these conditions *[see Contraindications (4)].* Immediately discontinue estradiol gel 0.1% if a PE, DVT, or stroke, occurs or is suspected. If feasible, discontinue estradiol gel 0.1% at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

The safety and efficacy of estradiol gel 0.1% for the prevention of cardiovascular disorders has not been established.

The Women's Health Initiate (WHI) estrogen-alone trial reported increased risks of pulmonary embolism (PE), deep vein thrombosis (DVT), and stroke, in postmenopausal women (50 to 79 years of age, average age 63.4 years) during 7.2 years of treatment with daily oral conjugated estrogen (CE) [0.625 mg] relative to placebo. Analyses were also conducted in women aged 50-59 years, a group of women more likely to present with onset of moderate to severe VMS compared to women of other age groups in the trial.

Only daily oral 0.625 mg CE was studied in the WHI estrogen-alone trial. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events to lower CE doses, other routes of administration, or other estrogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products *[see Clinical Studies (14.2)].*

Venous Thromboembolism

In women aged 50-59 years, the WHI estrogen-alone trial reported a relative risk for PE of 1.53 (95% confidence interval [CI], 0.63, 3.75) for CE compared to placebo, with an absolute risk difference of 4 per 10,000 women-years (WYs; 10 versus 6). The relative risk for DVT was 1.66 (95% CI 0.75, 3.67) for CE compared to placebo, with a risk difference of 5 per 10,000 WYs (13 versus 8).

In the overall study population of women aged 50-79 years, the WHI estrogen-alone trial reported a relative risk of PE of 1.35 (95% CI 0.89, 2.05) for CE compared to placebo, with a risk difference of 4 per 10,000 WYs (14 versus 10). The relative risk for DVT was 1.48 (95% 1.06, 2.07) for CE compared to placebo, with a risk difference of 7 per 10,000 WYs (23 versus 15) *[see Clinical Studies (14.2)].*

Stroke

In women aged 50-59 years, the WHI estrogen-alone trial reported a relative risk for stroke of 0.99 (95% 0.53, 1.85) for CE compared to placebo, with a risk difference of -1 per 10,000 WYs (16 versus 17).

In the overall study population of women aged 50-79 years, the WHI estrogen-alone trial reported a relative risk for stroke of 1.35 (95%, 1.07, 1.70) for CE compared to placebo, with a risk difference of 11 per 10,000 WYs (45 versus 34) *[see Clinical Studies (14.2)].*

5.2 Malignant Neoplasms

Endometrial Cancer

In estradiol gel 0.1%-treated menopausal women with a uterus with persistent or recurring abnormal genital bleeding of unknown etiology, perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to assess for endometrial cancer.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

Adding a progestogen to estrogen-alone therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. There are, however, possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens *[see Warnings and Precautions (5.3)].*

Breast Cancer

Surveillance measures for breast cancer, such as breast examinations and mammography, are recommended. The use of estrogen-alone therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

In the WHI estrogen-alone trial, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer. Among women 50-59 years old, the relative risk was 0.82 (95% CI, 0.50, 1.34) for CE compared to placebo, with a risk difference of -5 per 10,000 WYs (24 versus 29). In the overall study population of women aged 50-79 years (average age 63.4 years), the relative risk was 0.79 (95% CI, 0.61, 1.02), with a risk difference of -7 per 10,000 WYs (28 versus 35). *[see Clinical Studies (14.2)]*.

However, a large meta-analysis including 24 prospective studies of postmenopausal women comparing current use of estrogen-only products with use duration of 5 to 14 years (average of 9 years) versus never use reported a relative risk for breast cancer of 1.33 (95% CI, 1.28 to 1.38).[1]

Ovarian Cancer

A large meta-analysis including 17 prospective studies of postmenopausal women compared current use of estrogen-only products versus never use and reported a relative risk for ovarian cancer of 1.37 (95% CI, 1.26 to 1.50). The duration of hormone therapy use that was associated with an increased risk of ovarian cancer is unknown.[2]

5.3 Risks Associated with Co-administration of Estrogen Plus Progestogen

Studies of the addition of a progestogen for 10 or more days of a cycle of estrogen

administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

If estradiol gel 0.1% is administered with a progestogen, there are possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens. Refer to prescribing information for progestogens indicated for the prevention of endometrial hyperplasia in non-hysterectomized women receiving estrogens.

5.4 Gallbladder Disease

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

5.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. Discontinue estrogens, including estradiol gel 0.1%, if hypercalcemia occurs, and take appropriate measures to reduce the serum calcium level.

5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue estradiol gel 0.1% pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Permanently discontinue estrogens, including estradiol gel 0.1%, if examination reveals papilledema or retinal vascular lesions.

5.7 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

5.8 Exacerbation of Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Discontinue estradiol gel 0.1% if pancreatitis occurs.

5.9 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any woman with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue estradiol gel 0.1%.

5.10 Exacerbation of Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more

thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. Monitor thyroid function in these women during treatment with estradiol gel 0.1% to maintain their free thyroid hormone levels in an acceptable range.

5.11 Fluid Retention

Estrogens may cause some degree of fluid retention. Monitor any woman with a condition(s) that might predispose her to fluid retention, such as a cardiac or renal impairment. Discontinue estrogen-alone therapy, including estradiol gel 0.1%, with evidence of medically concerning fluid retention.

5.12 Hypocalcemia

Estrogen-induced hypocalcemia may occur in women with hypoparathyroidism. Consider whether the benefits of estrogen therapy outweigh the risks in such women.

5.13 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. Consider the addition of a progestogen therapy for a woman known to have residual endometriosis post-hysterectomy.

5.14 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy, including estradiol gel 0.1%, outweigh the risks in such women.

5.15 Exacerbation of Other Conditions

Estrogen therapy, including estradiol gel 0.1%, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks in women with such conditions.

5.16 Photosensitivity

The effects of direct sun exposure to estradiol gel 0.1% application sites have not been evaluated in clinical trials.

5.17 Application of Sunscreen and Topical Solutions

Studies conducted using other approved topical estrogen gel products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels.

The effect of sunscreens and other topical lotions on the systemic exposure of estradiol gel 0.1% has not been evaluated in clinical trials.

5.18 Flammability of Alcohol-Based Gels

Alcohol based gels are flammable. Avoid fire, flame, or smoking until estradiol gel 0.1% has dried.

Occlusion of the area where the topical drug product is applied with clothing or other barriers is not recommended until estradiol gel 0.1% has completely dried.

5.19 Potential for Estradiol Transfer and Effects of Washing

There is a potential for drug transfer from one individual to the other following physical contact of estradiol gel 0.1% application sites. In a study to evaluate transferability to males from their female contacts, there was some elevation of estradiol levels over baseline in the male subjects; however, the degree of transferability in this study was inconclusive. Women are advised to avoid skin contact with other persons until the gel is completely dried. The site of application should be covered (clothed) after drying.

Washing the application site with soap and water 1 hour after application resulted in a 30 to 38 percent decrease in the mean total 24-hour exposure to estradiol. Therefore, women should refrain from washing the application site for at least one hour after application.

5.20 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels are not useful in the management of moderate to severe vasomotor symptoms.

5.21 Drug-Laboratory Test Interactions

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin).
- Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels.
- Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.1)].*
- Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions (5.2)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Estradiol gel 0.1% was studied at doses of 0.25, 0.5 and 1.0 gram per day in a 12-week, double-blind, placebo-controlled study that included a total of 495 postmenopausal women (86.5 percent Caucasian). The adverse reactions that occurred at a rate greater than 5 percent and greater than placebo in any of the treatment groups are summarized in Table 1.

Table 1: Number (%) of Subjects with Common Adverse Reactions* in a 12-Week Placebo-Controlled Study of Estradiol Gel 0.1%

	Estradiol Gel 0.1%			Placebo
SYSTEM ORGAN CLASS Preferred Term	**0.25 grams/day N=122 n (%)**	**0.5 grams/day N=123 n (%)**	**1.0 gram/day N=125 n (%)**	**N=125 n (%)**
INFECTIONS & INFESTATIONS				
Nasopharyngitis	7 (5.7)	5 (4.1)	6 (4.8)	5 (4.0)
Upper Respiratory Tract Infection	7 (5.7)	3 (2.4)	2 (1.6)	2 (1.6)
Vaginal mycosis	1 (0.8)	3 (2.4)	8 (6.4)	4 (3.2)
REPRODUCTIVE SYSTEM & BREAST DISORDERS				
Breast Tenderness	3 (2.5)	7 (5.7)	11 (8.8)	2 (1.6)
Metrorrhagia	5 (4.1)	7 (5.7)	12 (9.6)	2 (1.6)

*Adverse reactions reported by >5 percent of patients in any treatment group.

In a 12-week placebo-controlled study of estradiol gel 0.1%, application site reactions were seen in <1 percent of participating women.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of estradiol gel 0.1%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System
Amenorrhea, dysmenorrhea, ovarian cyst, vaginal discharge

Breasts
Gynecomastia

Cardiovascular

Palpitations, ventricular extrasystoles

Gastrointestinal
Flatulence

Skin
Rash pruritic, urticaria

Eyes
Retinal vein occlusion

Central Nervous System
Tremor

Miscellaneous
Arthralgia, application site rash, asthenia, chest discomfort, fatigue, feeling abnormal, heart rate increased, insomnia, malaise, muscle spasms, pain in extremity, weight increased

7 DRUG INTERACTIONS

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and result in adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Estradiol gel 0.1% is not indicated for use in pregnant women. There are no data with the use of estradiol gel 0.1% in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogen and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary
Estrogens are present in human milk and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for estradiol gel 0.1% and any potential adverse effects on the breastfed child from estradiol gel 0.1% or from the underlying maternal condition.

8.4 Pediatric Use

Estradiol gel 0.1% is not indicated for use in pediatric patients. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing estradiol gel 0.1% to determine whether those over 65 years of age differ from younger subjects in their response to estradiol gel 0.1%.

The Women's Health Initiative Studies

In the WHI estrogen-alone trial (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.2)].*

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of probable dementia in women receiving estrogen-alone *[see Clinical Studies (14.3)].*

Since the trial was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Clinical Studies (14.3)]*. The safety and efficacy of estradiol gel 0.1% for the prevention of dementia has not been established.

10 OVERDOSAGE

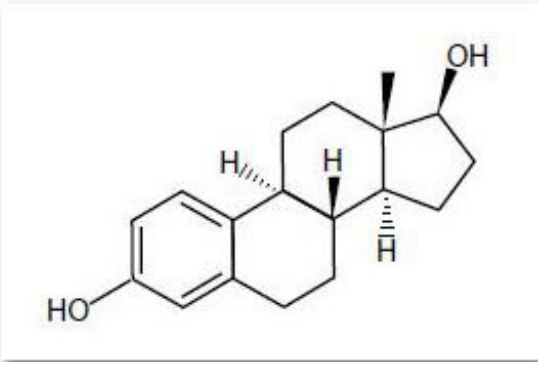
Overdosage of estrogen may cause nausea and vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding in women. Treatment of overdose consists of discontinuation of estradiol gel 0.1% therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

Estradiol gel 0.1%, is a clear, colorless gel, which is odorless when dry. It is designed to deliver sustained circulating concentrations of estradiol when applied once daily to the skin. The gel is applied to a small area (200 cm^2) of the thigh in a thin layer. Estradiol gel 0.1% is available in five doses of 0.25, 0.5, 0.75, 1.0, and 1.25 grams for topical application (corresponding to 0.25, 0.5, 0.75, 1.0, and 1.25 mg estradiol, respectively).

The active component of the topical gel is estradiol, an estrogen.

Estradiol is a white crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17ß-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:



The remaining components of the gel (carbomer, ethanol, propylene glycol, purified water, and triethanolamine) are pharmacologically inactive.

Estradiol gel 0.1% contains: 58.6% alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

Generally, a serum estrogen concentration does not predict an individual woman’s therapeutic response to estradiol gel 0.1% nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

12.3 Pharmacokinetics

Absorption

Estradiol diffuses across intact skin and into the systemic circulation by a passive absorption process, with diffusion across the stratum corneum being the rate-limiting factor.

In a 14-day, Phase 1, multiple-dose study, estradiol gel 0.1% demonstrated linear and approximately dose- proportional estradiol pharmacokinetics at steady state for both AUC_{0-24} and C_{max} following once daily dosing to the skin of either the right or left upper thigh (Table 2).

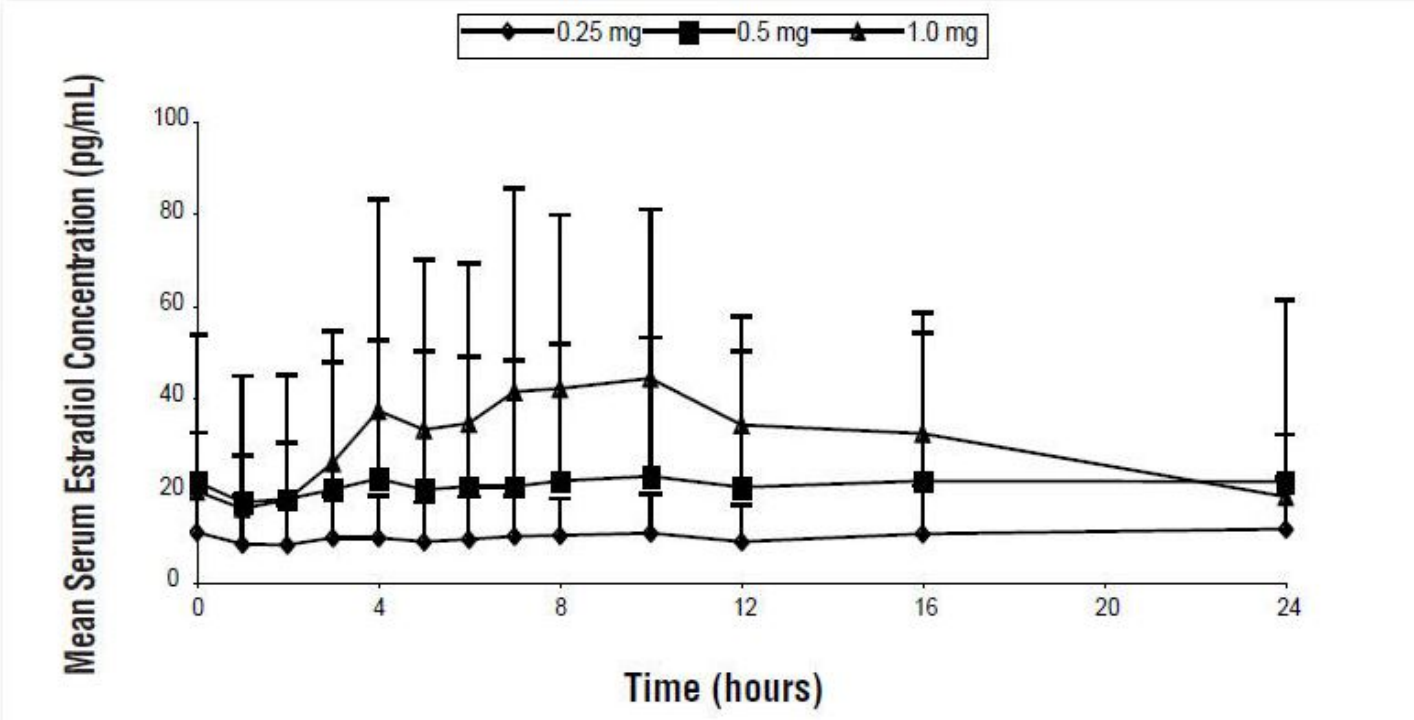
Table 2: Mean (%CV) Pharmacokinetic Parameters for Estradiol (uncorrected for baseline) on Day 14 Following Multiple Daily Doses of Estradiol Gel 0.1%

Parameter (units)	Estradiol Gel 0.25 grams	Estradiol Gel 0.5 grams	Estradiol Gel 1.0 gram
AUC_{0-24} (pg•h/mL)	236 (94)	504 (149)	732 (81)
C_{max} (pg/mL)	14.7 (84)	28.4 (139)	51.5 (86)
C_{avg} (pg/mL)	9.8 (92)	21 (148)	30.5 (81)
t_{max} * (h)	16 (0,72)	10 (0,72)	8 (0,48)
E2:E1 ratio	0.42	0.65	0.65

*Median (Min, Max).

Steady-state serum concentration of estradiol are achieved by day 12 following daily application of estradiol gel 0.1% to the skin of the upper thigh. The mean (SD) serum estradiol levels following once daily dosing at day 14 are shown in Figure 1.

Figure 1: Mean (SD) Serum Estradiol Concentrations (Values Uncorrected for Baseline) on Day 14 Following Multiple Daily Doses of Estradiol Gel 0.1%



The effect of sunscreens and other topical lotions on the systemic exposure of estradiol gel 0.1% has not been evaluated. Studies conducted using topical estrogen gel approved

products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels.

Distribution

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

Metabolism

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

Although the clinical significance has not been determined, estradiol from estradiol gel 0.1% does not undergo first pass metabolism and provides estradiol to estrone ratios at steady state in the range of 0.42 to 0.65.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The apparent terminal half-life for estradiol was about 10 hours following administration of estradiol gel 0.1%.

Potential for Estradiol Transfer

The effect of estradiol transfer was evaluated in healthy postmenopausal women who topically applied 1.0 gram of estradiol gel 0.1% (single dose) on one thigh. One and 8 hours after gel application, they engaged in direct thigh-to-arm contact with a partner for 15 minutes. While some elevation of estradiol levels over baseline was seen in the male subjects, the degree of transferability in this study was inconclusive.

Effects of Washing

The effect of application site washing on skin surface levels and serum concentrations of estradiol was determined in 16 healthy postmenopausal women after application of 1.0 gram of estradiol gel 0.1% to a 200 cm^2 area on the thigh. Washing the application site with soap and water 1 hour after application removed all detectable amounts of estradiol from the surface of the skin and resulted in a 30 to 38 percent decrease in the mean total 24-hour exposure to estradiol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

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.

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms in Postmenopausal Women

A randomized, double-blind, placebo-controlled trial evaluated the efficacy of 12-week treatment with three different daily doses of estradiol gel 0.1% for vasomotor symptoms in 495 postmenopausal women (86.5 percent White; 10.1 percent Black) between 34 and 89 years of age (mean age 54.6) who had at least 50 moderate to severe hot flushes per week at baseline (2-week period prior to treatment). Women applied placebo, estradiol gel 0.1% 0.25 grams (0.25 mg estradiol), estradiol gel 0.1% 0.5 grams (0.5 mg estradiol) or estradiol gel 0.1% 1.0 gram (1.0 mg estradiol) once daily to the thigh. Reductions in both the median daily frequency and the median daily severity of moderate to severe hot flushes were statistically significant for the 0.5 grams per day and the 1.0 gram per day estradiol gel 0.1% doses when compared to placebo at week 4. Statistically significant reductions in both the median daily frequency and the median daily severity of moderate to severe hot flushes for the estradiol gel 0.1% 0.25 grams per day dose when compared to placebo were delayed to week 7. There were statistically significant reductions in median daily frequency and severity of hot flushes for all three estradiol gel 0.1% doses (0.25 grams per day, 0.5 grams per day and 1.0 gram per day) compared to placebo at week 12. See Table 3 for results.

Table 3: Summary of Change From Baseline in the Median Daily Frequency and Severity of Hot Flushes during Estradiol Gel 0.1% Treatment (ITT Population)

	Estradiol Gel 0.1%			**Placebo**
Evaluation	0.25 grams/day N=121	0.5 grams/day N=119	1.0 gram/day N=124	N=124
Frequency of Daily Hot Flushes				
Baseline Median	9.72	9.24	9.64	9.32
Median Change: Week 4	-5.00	-5.73	-7.20	-3.63
p-value†	0.132	0.011	<0.001	
Median Change: Week 7	-6.62	-7.14	-7.71	-4.37
p-value†	<0.001	<0.001	<0.001	
Median Change: Week 12	-6.88	-7.29	-8.35	-4.48
p-value†	<0.001	<0.001	<0.001	
Severity of Daily Hot Flushes				
Baseline Median	2.52	2.51	2.52	2.54
Median Change: Week 4	-0.07	-0.18	-0.47	-0.04
p-value†	0.283	<0.001	<0.001	
Median Change: Week 7	-0.24	-0.46	-1.06	-0.06
p-value†	<0.001	<0.001	<0.001	
Median Change: Week 12	-0.33	-0.56	-1.69	-0.13
p-value†	0.021	0.002	<0.001	

†p-values from the van Elteren's test stratified by pooled center; comparison in median change was significant if $p<0.05$.

14.2 Women's Health Initiative Estrogen-Alone Trial

The WHI estrogen-alone trial enrolled predominantly healthy postmenopausal women in trial to assess the risks and benefits of daily oral CE (0.625 mg)-alone compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other cause. This trial did not evaluate the effects of CE- alone on menopausal symptoms.

The WHI estrogen-alone trial was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints. Centrally adjudicated results for stroke events, after an average follow-up of 7.1 years, reported estrogen-alone increased the risk for ischemic stroke compared to placebo, and this excess risk was present in all subgroups of women examined.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared to placebo was reported in final centrally adjudicated results from the estrogen-alone trial, after an average follow-up of 7.1 years.[3,4]

Results of the estrogen-alone trial, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), after an average follow-up of 7.1 years are presented in Table A.

Table A: Relative Risk and Risk Difference Observed in the WHI Estrogen-Alone Trial at an Average of 7.1 Years of Follow-up[a]

Event	Relative Ratio (95% CI)[c]	Risk Difference (CE vs placebo/10,000 WYs)
CHD events	0.94 (0.78-1.14)	-3 (55 vs 58)
Non-fatal MI	*0.97 (0.79-1.21)*	*-1 (44 vs 45)*
CHD death	*1.00 (0.77-1.31)*	*0 (29 vs 29)*
All Strokes	1.35 (1.07-1.70)	11 (45 vs 34)
Deep vein thrombosis[d]	1.48 (1.06-2.07)	7 (23 vs 15)
Pulmonary embolism	1.35 (0.89-2.05)	4 (14 vs 10)
Invasive breast cancer[e]	0.79 (0.61-1.02)	-7 (28 vs 35)
Colorectal cancer	1.15 (0.81-1.64)	2 (17 vs 15)
Hip fracture	0.67 (0.46-0.96)	-6 (13 vs 19)
Vertebral fractures[d]	0.64 (0.44-0.93)	-6 (12 vs 18)
Total fractures[d]	0.72 (0.64-0.80)	-61 (153 vs 214)
Overall mortality[c,f]	1.03 (0.88-1.21)	3 (80 vs 77)
Global Index[g]	1.03 (0.93-1.13)	4 (208 vs 204)

[a] Adapted from 2013 WHI trial (CE n=5,310, placebo n=5,429). WHI publications can be

viewed at www.nhlbi.nih.gov/whi.

[b] Results are based on centrally adjudicated data.

[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards models comparing treatment to placebo; however, they are described here as relative risks. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[d] Not included in "global index."

[e] Includes metastatic and non-metastatic breast cancer with the exception of in situ cancer.

[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

[g] Asubset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen-alone therapy to the start of menopause may affect the overall risk benefit profile. The study results for women 50-59 years old in the WHI estrogen-alone trial are shown in Table B.

Table B: Relative Risk and Risk Difference Observed Among Women 50-59 Years of Age in the WHI Estrogen-Alone Trial at an Average of 7.1 Years[a,b]

Event	Relative Ratio (95% CI)[c]	Risk Difference (CE vs placebo/10,000 WYs)
CHD events	0.60 (0.35-1.04)	-11 (17 vs 28)
Non-fatal MI	*0.55 (0.31-1.00)*	*-11 (14 vs 25)*
CHD death	*0.80 (0.32-2.04)*	*-1 (7 vs 8)*
All Strokes	0.99 (0.53-1.85)	-1 (16 vs 17)
Deep vein thrombosis[d]	1.66 (0.75-3.67)	5 (13 vs 8)
Pulmonary embolism	1.53 (0.63-3.75)	4 (10 vs 6)
Invasive breast cancer[e]	0.82 (0.50-1.34)	-5 (24 vs 29)
Colorectal cancer	0.71 (0.30-1.67)	-3 (7 vs 10)
Hip fracture	5.01 (0.59-42.91)	3 (1 vs 3)
Vertebral fractures[d]	0.50 (0.17-1.47)	-4 (4 vs 8)
Total fractures[d]	0.90 (0.72-1.11)	-16 (133 vs 149)
Overall mortality[c,f]	0.70 (0.46-1.09)	-11 (29 vs 40)
Global Index[g]	0.84 (0.66-1.07)	-19 (98 vs 117)

[a] Adapted from 2013 WHI trial (CE n=1,639, placebo n=1,674). WHI publications can be viewed at www.nhlbi.nih.gov/whi.

[b] Results are based on centrally adjudicated data.

[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards

models comparing treatment to placebo; however, they are described here as relative risks. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[d] Not included in “global index.”

[e] Includes metastatic and non-metastatic breast cancer with the exception of in situ cancer.

[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

[g] A subset of the events was combined in a “global index,” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other causes.

14.3 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age (45% were 65 to 69 years of age, 36% were 70 to 74 years of age, and 19% were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo. Probable dementia as defined in this study included Alzheimer’s disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95% CI, 0.83– 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.[5]

15 REFERENCES

1. Lancet. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. 2019 Sep 28;394(10204):1159-1168.
2. Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R. Collaborative Group On Epidemiological Studies Of Ovarian Cancer; Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 2015 May 9;385(9980):1835-42.
3. Anderson GL, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004 Apr 14;291(14):1701-12.
4. Manson, J. E., et al Menopausal hormone therapy and health outcomes during the intervention and extended post stopping phases of the Women's Health Initiative randomized trials. JAMA, 310(13): 1353–1368 (2013).
5. Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, Hsia J, Margolis KL, Hogan PE, Wallace R, Dailey M, Freeman R, Hays J; Women's Health

Initiative Memory Study. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2959-68.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Estradiol gel 0.1% is a clear, colorless, smooth, opalescent gel supplied in single-dose foil packets of 0.25, 0.5, 0.75, 1.0, and 1.25 grams, corresponding to 0.25, 0.5, 0.75, 1.0, and 1.25 mg estradiol, respectively.

NDC 70700-143-35, carton of 30 packets, 0.25 mg estradiol per single-dose foil packet

NDC 70700-144-35, carton of 30 packets, 0.5 mg estradiol per single-dose foil packet

NDC 70700-194-35, carton of 30 packets, 0.75 mg estradiol per single-dose foil packet

NDC 70700-145-35, carton of 30 packets, 1.0 mg estradiol per single-dose foil packet

NDC 70700-195-35, carton of 30 packets, 1.25 mg estradiol per single-dose foil packet

Keep out of the reach of children.

16.2 Storage and Handling

Store at 20 to 25°C (68 to 77°F). Excursions permitted to 15 to 30°C (59 to 86°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

Advise women to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Vaginal Bleeding

Inform postmenopausal women to report any vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.2)].*

Unintentional Secondary Exposure to Estradiol Gel 0.1%

Inform women about the possibility of secondary exposure to estradiol gel 0.1%:

- Apply estradiol gel 0.1% as directed and keep children from contacting exposed application site(s). If direct contact with the application site occurs, wash the contact area thoroughly with soap and water.
- Look for signs of unexpected sexual development, such as breast mass or increased breast size in prepubertal children.
- If signs of unintentional secondary exposure are noticed:
- Have the child(ren) evaluated by a healthcare provider.

- Have women contact their healthcare provider to discuss the appropriate use and handling of estradiol gel 0.1% when around children.
- Pets may also be unintentionally exposed to estradiol gel 0.1% if above precautions are not followed.

Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders and Malignant Neoplasms *[see Warnings and Precautions (5.1, 5.2)].*

Possible Less Serious but Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headaches, breast pain and tenderness, nausea and vomiting.

PATIENT INFORMATION

Estradiol gel 0.1%

Read this Patient Information leaflet before you start using estradiol gel 0.1% and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ESTRADIOL GEL 0.1% (AN ESTROGEN HORMONE)?

- Using estrogen-alone increases your chance of getting cancer of the uterus (womb).
- Report any unusual vaginal bleeding right away while you are using estradiol gel 0.1%. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline of brain function)
- Using estrogen-alone may increase your chances of getting strokes or blood clots
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia.

Because other products and doses have not been studied in the same way, it is not known how the use of estradiol gel, 0.1% will affect your chances of these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with estradiol gel 0.1%.

What is estradiol gel 0.1%?

Estradiol gel 0.1% is a prescription medicine that contains estradiol (an estrogen hormone). Estradiol gel 0.1% is a clear, colorless, smooth gel that is odorless when dry. When applied to the skin, estradiol is absorbed through the skin into the bloodstream.

What is estradiol gel 0.1% used for?

Estradiol gel 0.1% is used after menopause to:

- Reduce moderate to severe hot flashes

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making

estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe.

Who should not use estradiol gel 0.1%?

Do not start using estradiol gel 0.1% if you:

- **have any unusual vaginal bleeding**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have been diagnosed with a bleeding disorder**
- **currently have or have had certain cancers**
  Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus (womb). If you have or have had cancer, talk with your healthcare provider about whether you should use estradiol gel 0.1%.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **are allergic to estradiol gel 0.1% or any of its ingredients**
  See the list of ingredients in estradiol gel 0.1% at the end of this leaflet.

Before you use estradiol gel 0.1%, tell your healthcare provider about all of your medical conditions, including if you:

- **have any unusual vaginal bleeding**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have any other medical conditions that may become worse while you are using estradiol gel 0.1%**
  Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraines, endometriosis, lupus, angioedema (swelling of face and tongue), problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **are going to have surgery or will be on bedrest**
  Your healthcare provider will let you know if you need to stop using estradiol gel 0.1%.
- **are pregnant or think you may be pregnant**
  Estradiol gel 0.1% is not for pregnant women.
- **are breastfeeding**
  The hormone in estradiol gel 0.1% can pass into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some

medicines may affect how estradiol gel 0.1% works. Estradiol gel 0.1% may also affect how your other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get new medicine.

How should I use estradiol gel 0.1%?

- Take the dose recommended by your healthcare provider and talk to him or her about how well that dose is working for you.
- Estrogens should be used at the lowest dose possible for your treatment and only as long as needed.

You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are using and whether you still need treatment with estradiol gel 0.1%.

How should estradiol gel 0.1% be applied?

- Estradiol gel 0.1% should be applied 1-time a day, around the same time each day.
- Apply estradiol gel 0.1% to clean, dry, and unbroken (without cuts or scrapes) skin. If you take a bath or shower, be sure to apply your estradiol gel 0.1% after your skin is dry. The application site should be completely dry before dressing or swimming.
- Apply estradiol gel 0.1% to either your left or right upper thigh. Change between your left and right upper thigh each day to help prevent skin irritation.

TO APPLY:

Step 1: Wash and dry your hands thoroughly.

Step 2: Sit in a comfortable position.

Step 3: Cut or tear the estradiol gel 0.1% packet as shown in Figure A.

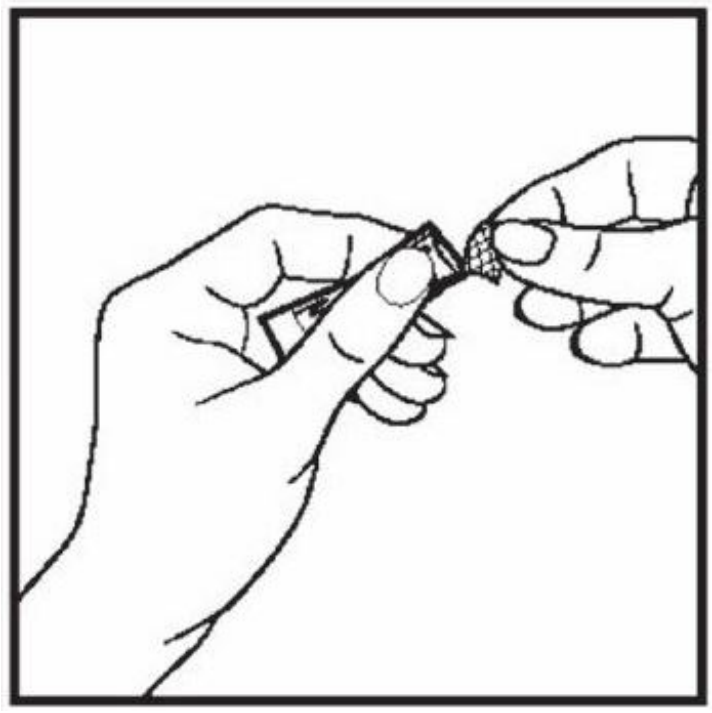


Figure A

Step 4: Using your thumb and pointer (index) finger, squeeze the entire contents of the estradiol gel 0.1% packet onto the skin of the upper thigh as shown in Figure B.

Figure B

Step 5: Gently spread the gel in a thin layer on your upper thigh over an area of about 5 by 7 inches, or two palm prints as shown in Figure C. It is not necessary to massage or rub in estradiol gel 0.1%.

Figure C

Step 6: Allow the gel to dry completely before dressing.

Step 7: Throw away (dispose) of the empty estradiol gel 0.1% packet in the trash.

Step 8: Wash your hands with soap and water immediately after applying estradiol gel 0.1% to remove any remaining gel and reduce the chance of transferring estradiol gel 0.1% to other people.

Important things to remember when using estradiol gel 0.1%

- Allow the gel to dry before dressing. Try to keep the area dry for as long as possible.
- Do not allow another person to come in contact with the area of skin where you applied the gel for at least 1 hour after you apply estradiol gel 0.1%.
- You should not have another person to apply the gel for you. However, if you need to have another person help you, have that person wear a disposable plastic glove to avoid direct contact with estradiol gel 0.1%.
- Do not apply estradiol gel 0.1% to your face, breast, or irritated skin.
- Never apply estradiol gel 0.1% in or around the vagina.
- **Estradiol gel 0.1% contains alcohol. Alcohol based gels are flammable. Avoid fire, flame or smoking until the gel has dried.**

What should I do if I miss a dose?

If you miss a dose, do not double the dose on the next day to catch up. If your next dose is less than 12 hours away, it is best just to wait and apply your normal dose the next day. If it is more than 12 hours until the next dose, apply the dose you missed and resume your normal dosing the next day. Do not apply estradiol gel 0.1% more than 1-time each day. If you accidentally spill some of the contents of an estradiol gel 0.1% packet, do not open a new estradiol gel 0.1% packet. Wait and apply your normal dose the next day.

What should I do if someone else is exposed to estradiol gel 0.1%?

To reduce the chance of transfer to another person (or pet) let the estradiol gel 0.1% dry completely. Wash your hands with soap and water after application. If someone else is exposed to estradiol gel 0.1% by direct contact with the wet gel, have that person wash the area of contact with soap and water right away. This is especially important for men and children. The longer the gel is in contact with the skin before washing, the greater the chance that the other person (or pet) will absorb some of the estrogen hormone. This may harm them. In case of any signs or symptoms of estrogen exposure in the other person (or pet), contact your healthcare provider (or veterinarian, if appropriate).

What should I do if I get estradiol gel 0.1% in my eyes?

If you get estradiol gel 0.1% in your eyes, flush your eyes right away with lukewarm tap water. If you have concerns, contact your healthcare provider.

What are the possible side effects of estradiol gel 0.1%?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- heart attack
- stroke
- blood clots
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- dementia
- high or low blood calcium (hypercalcemia)
- gall bladder disease
- visual abnormalities
- high blood pressure
- high levels of fat (triglycerides) in your blood
- liver problems
- changes in your thyroid hormone levels
- fluid retention
- cancer change of endometriosis
- enlargement of benign tumors of the uterus ("fibroids")
- worsening swelling of face and tongue (angioedema)
- changes in certain laboratory test results such as high blood sugar

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness, and fatigue
- swelling of face, lips, and tongue with or without red, itchy bumps

The most common side effects of estradiol gel 0.1% include:

- irregular vaginal bleeding or spotting
- breast tenderness
- vaginal yeast infection
- upper respiratory tract (nose, sinuses, pharynx or larynx) infection

These are not all the possible side effects of estradiol gel 0.1%. For more information, ask your healthcare provider or pharmacist for advice about side effects. Tell your healthcare provider if you have any side effects that bother you or do not go away.

You may report side effects to Xiromed, LLC. at 844-XIROMED (844-947-6633) or to

FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with estradiol gel 0.1%?

- Talk with your healthcare provider regularly about whether you should continue using estradiol gel 0.1%.
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestogen is right for you.
- See your healthcare provider right away if you get vaginal bleeding while using estradiol gel 0.1%.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else.
- If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances of getting heart disease.

Ask your healthcare provider for ways to lower your chances of getting heart disease.

How should I store estradiol gel 0.1%?

Store estradiol gel 0.1% packets at room temperature, 68° to 77 °F (20° to 25 °C).

Keep estradiol gel 0.1% and all medicines out of the reach of children.

General information about safe and effective use of estradiol gel 0.1%.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use estradiol gel 0.1% for a condition for which it was not prescribed. Do not give estradiol gel 0.1% to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet provides a summary of the most important information about estradiol gel 0.1%. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about estradiol gel 0.1% that is written for health professionals.

What are the ingredients in estradiol gel 0.1%?

Active ingredient: estradiol.

Inactive ingredients: carbomer, ethanol, propylene glycol, purified water, and triethanolamine.

Contains: 58.6% alcohol.

How is estradiol gel 0.1% Supplied?

Estradiol gel 0.1% is supplied in individual foil packets, each one containing a single day's dose.

Manufactured for:

Xiromed, LLC

Florham Park, NJ 07932

www.xiromed.com

Manufactured by:

Laboratorios Leon Farma, S.A.

Villaquilambre, Leon, Spain 24193

Customer Service: **844-XIROMED (844-947-6633)**

PI-145-04

Revised: 02/2026

This Patient Information has been approved by the U.S. Food and Drug Administration.

PRINCIPAL DISPLAY PANEL

PRINCIPAL DISPLAY PANEL - 1.25 mg Packet Carton

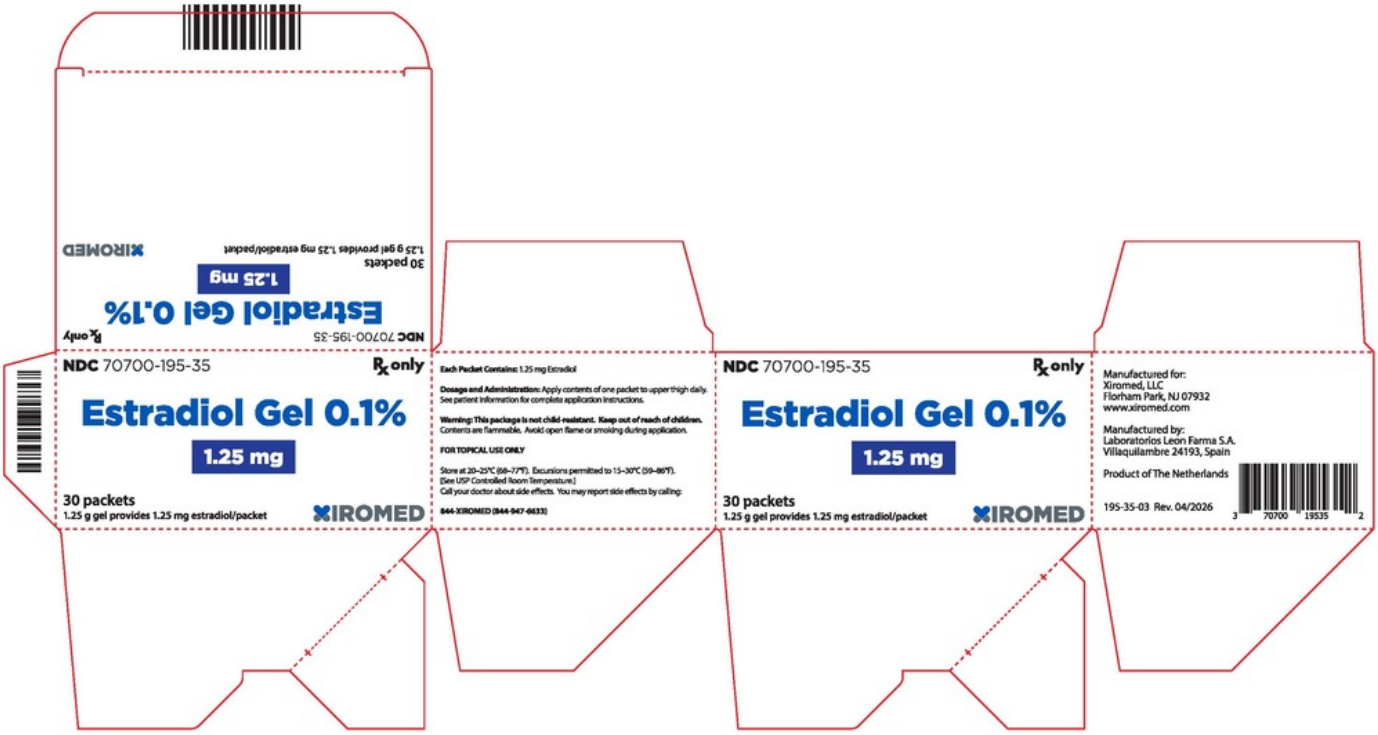
NDC 70700-195-35

Estadiol Gel 0.1% - **1.25 mg**

30 packets
1.25 g gel provides 1.25 mg estradiol/packet

Rx only

Xiromed LLC.



PRINCIPAL DISPLAY PANEL - 1 mg Packet Carton

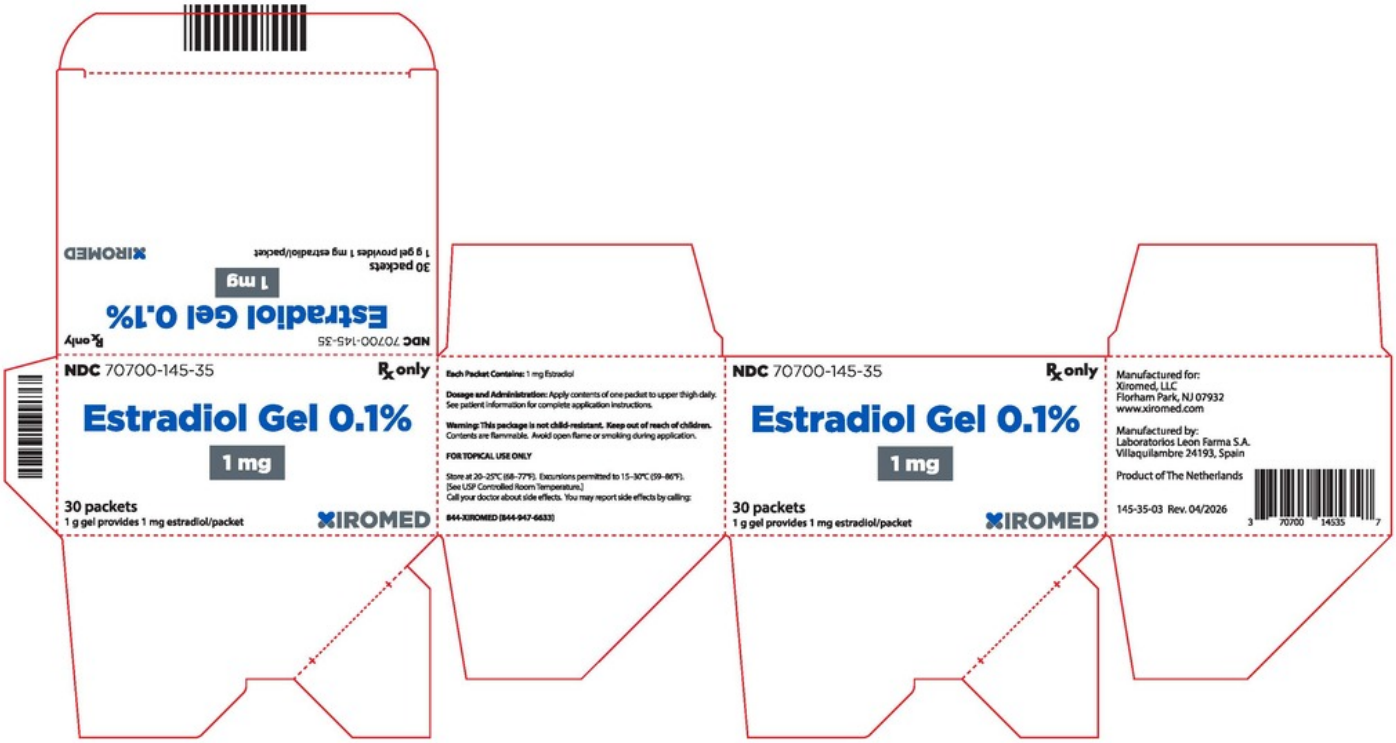
NDC 70700-145-35

Estadiol Gel 0.1% - **1 mg**

30 packets
1 g gel provides 1 mg estradiol/packet

Rx only

Xiromed LLC.



PRINCIPAL DISPLAY PANEL - 0.75 mg Packet Carton

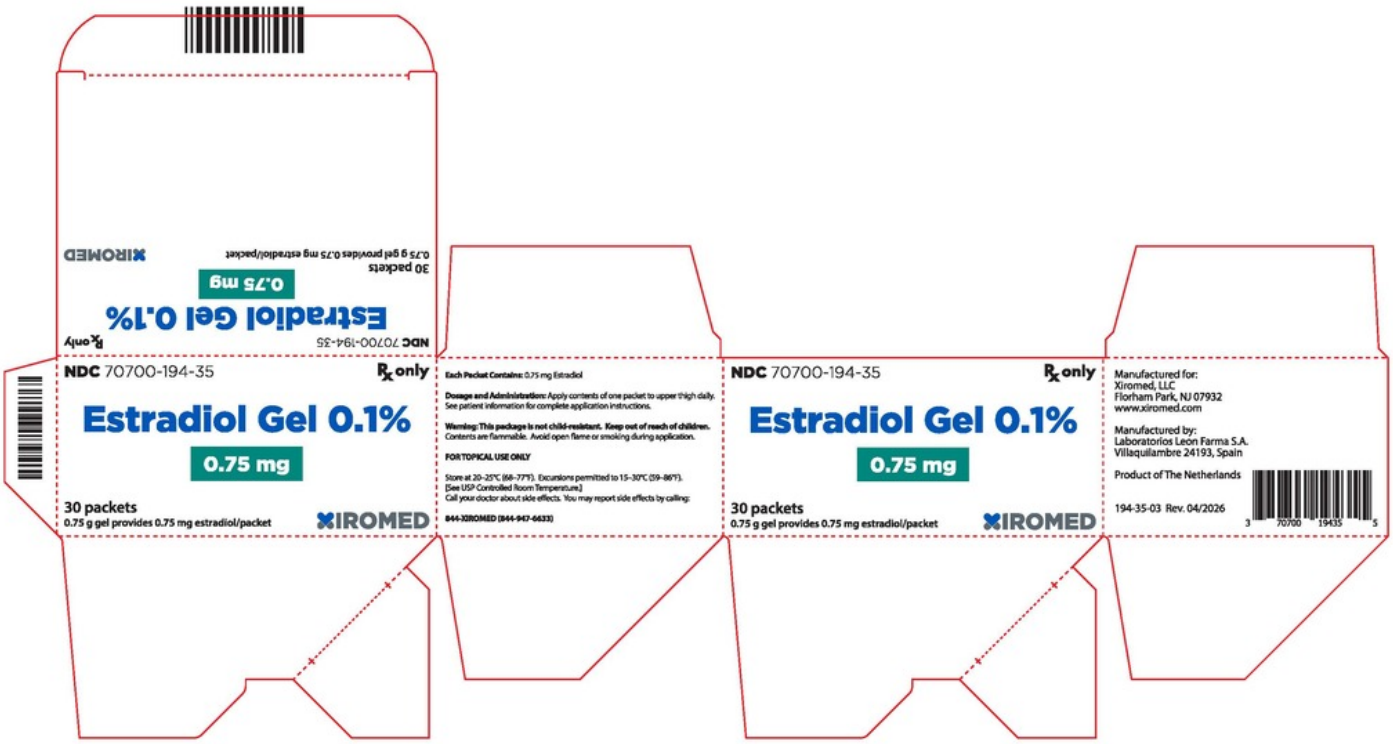
NDC 70700-194-35

Estadiol Gel 0.1% - **0.75 mg**

30 packets
0.75 g gel provides 0.75 mg estradiol/packet

Rx only

Xiromed LLC.



PRINCIPAL DISPLAY PANEL

PRINCIPAL DISPLAY PANEL - 0.5 mg Packet Carton

NDC 70700-144-35

Estradiol Gel 0.1%- 0.5 mg

30 packets
0.5 g gel provides 0.5 mg estradiol/packet

Rx only

Xiromed LLC.

PRINCIPAL DISPLAY PANEL

PRINCIPAL DISPLAY PANEL - 0.25 mg Packet Carton

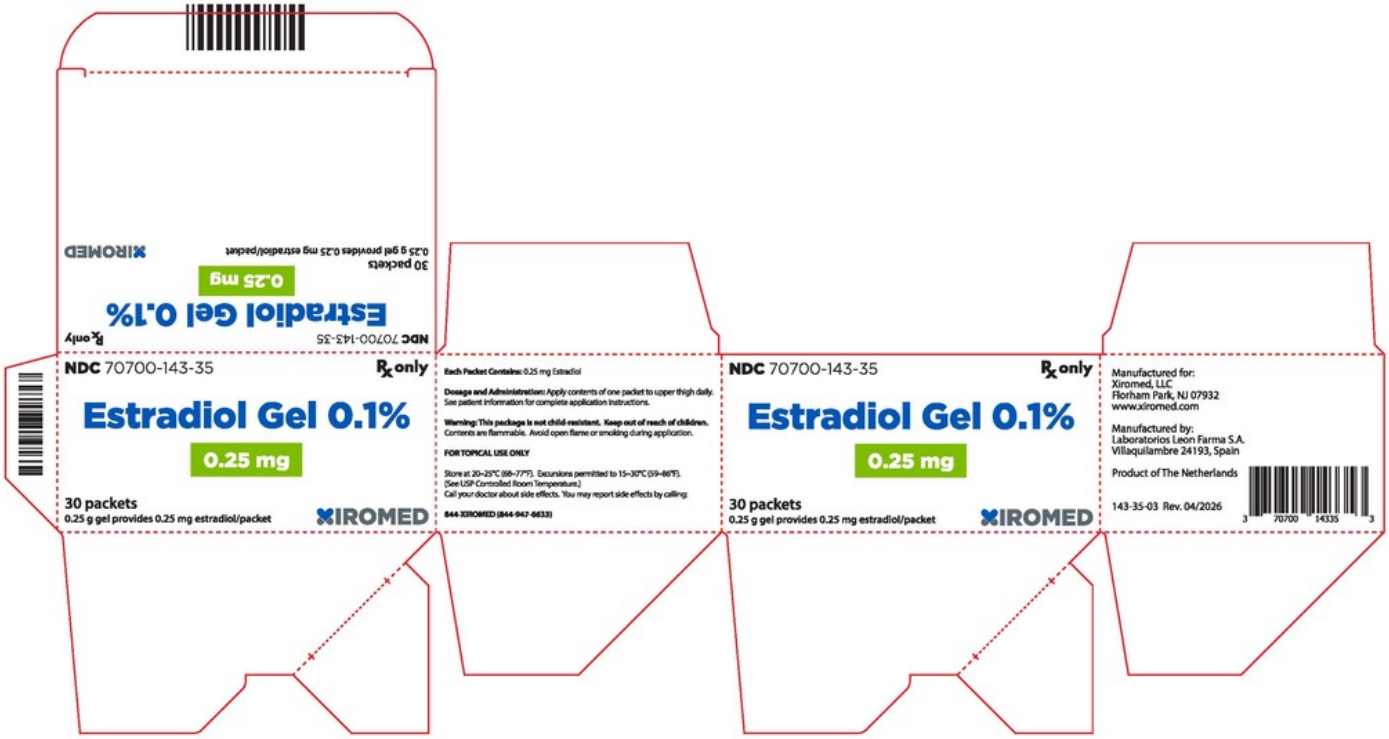
NDC 70700-143-35

Estradiol Gel 0.1% - 0.25 mg

30 packets
0.25 g gel provides 0.25 mg estradiol/packet

Rx only

Xiromed, LLC.



ESTRADIOL

estradiol gel 0.1% gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70700-143
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.25 mg in 0.25 g

Inactive Ingredients	
Ingredient Name	**Strength**
Carbomer Homopolymer Type B (Allyl Pentaerythritol Or Allyl Sucrose Crosslinked) (UNII: K6MOM3T5YL)	
ALCOHOL (UNII: 3K9958V90M)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
TROLAMINE (UNII: 9O3K93S3TK)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:70700-143-35	30 in 1 CARTON	10/01/2022	

1		0.25 g in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211783	10/01/2022	

ESTRADIOL

estradiol gel 0.1% gel

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70700-144
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.5 mg in 0.5 g

Inactive Ingredients

Ingredient Name	Strength
Carbomer Homopolymer Type B (Allyl Pentaerythritol Or Allyl Sucrose Crosslinked) (UNII: K6MOM3T5YL)	
ALCOHOL (UNII: 3K9958V90M)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
TROLAMINE (UNII: 9O3K93S3TK)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70700-144-35	30 in 1 CARTON	10/01/2022	
1		0.5 g in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211783	10/01/2022	

ESTRADIOL

estradiol gel 0.1% gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70700-194
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.75 mg in 0.75 g

Inactive Ingredients	
Ingredient Name	**Strength**
Carbomer Homopolymer Type B (Allyl Pentaerythritol Or Allyl Sucrose Crosslinked) (UNII: K6MOM3T5YL)	
ALCOHOL (UNII: 3K9958V90M)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
TROLAMINE (UNII: 9O3K93S3TK)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:70700-194-35	30 in 1 CARTON	10/01/2022	
1		0.75 g in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211783	10/01/2022	

ESTRADIOL

estradiol gel 0.1% gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70700-145
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	1 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
Carbomer Homopolymer Type B (Allyl Pentaerythritol Or Allyl Sucrose Crosslinked) (UNII: K6MOM3T5YL)	
ALCOHOL (UNII: 3K9958V90M)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
TROLAMINE (UNII: 9O3K93S3TK)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:70700-145-35	30 in 1 CARTON	10/01/2022	
1		1 g in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211783	10/01/2022	

ESTRADIOL

estradiol gel 0.1% gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70700-195
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	1.25 mg in 1.25 g

Inactive Ingredients	
Ingredient Name	**Strength**
Carbomer Homopolymer Type B (Allyl Pentaerythritol Or Allyl Sucrose Crosslinked) (UNII: K6MOM3T5YL)	
ALCOHOL (UNII: 3K9958V90M)	

PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
TROLAMINE (UNII: 9O3K93S3TK)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70700-195-35	30 in 1 CARTON	10/01/2022	
1		1.25 g in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211783	10/01/2022	

Labeler - Xiromed, LLC (080228637)

Registrant - Chemo Research, S.L. (464268393)

Establishment

Name	Address	ID/FEI	Business Operations
Laboratorios Leon Farma		467782459	manufacture(70700-143, 70700-144, 70700-145, 70700-194, 70700-195) , pack(70700-145, 70700-144, 70700-143, 70700-194, 70700-195) , label(70700-145, 70700-144, 70700-143, 70700-194, 70700-195) , analysis(70700-145, 70700-144, 70700-143, 70700-194, 70700-195)

Revised: 5/2026 Xiromed, LLC