PRODUCT MONOGRAPH

ESTROGEL PROPAK™

17ß-estradiol, as estradiol hemihydrate
Transdermal gel
0.06%

Progesterone capsules
100 mg

Estrogen and Progestin

Merck Canada Inc.
16750 route Transcanadienne
Kirkland QC Canada H9H 4M7
http://www.merck.ca

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
ESTROGEL®		
Transdermal	Gel 0.06%	Carbopol 980, triethanolamine, ethanol and purified water.
PROMETRIUM®		
oral	capsule 100 mg	Soya lecithin (may contain traces of medium chain triglycerides) *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ESTROGEL PROPAK™ (17ß-estradiol and micronized progesterone) is indicated in patients for whom treatment with both ESTROGEL® and PROMETRIUM® is appropriate.

ESTROGEL®

ESTROGEL® (17ß-estradiol) is indicated for:

- replacement therapy in naturally occurring or surgically induced estrogen deficiency states associated with menopausal and postmenopausal symptoms, e.g. hot flushes, sleep disturbances and atrophic vaginitis.

ESTROGEL® should be prescribed with an appropriate dosage of progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

Geriatrics: No clinical studies were conducted to evaluate the effect of ESTROGEL® on women more than 65 years old.

Pediatrics: ESTROGEL® should not be used in children.

PROMETRIUM®

PROMETRIUM (micronized progesterone) is indicated for:

- women with an intact uterus as an adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma.

CONTRAINDICATIONS

ESTROGEL PROPAK™ (17ß-estradiol and micronized progesterone) is contraindicated in patients with any of the following disorders:

- hypersensitivity to this drug, soya, peanut or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph;
- active hepatic dysfunction or disease, especially of the obstructive type or liver dysfunction or disease as long as liver function tests have failed to return to normal;
- personal history of known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g. breast cancer or endometrial cancer)
- endometrial hyperplasia;
- undiagnosed abnormal genital bleeding;
- known or suspected pregnancy;
- active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease (CHD))
- classical migraine;
- active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis;
- partial or complete loss of vision due to ophthalmic vascular disease;
- breast-feeding

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years. [4, 49, 54]

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 embolism 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. [54]

The *estrogen-alone* arm of the WHI trial (mean age 63.3 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. [49]

The Women's Health Initiative Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older.

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases or dementia.
- 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.

General

Effects on ability to drive and use machines

Transient and occasional somnolence or dizziness may occur in some patients 1-4 hours after ingestion of PROMETRIUM®, particularly if administered with food. Activities requiring concentration, good attention, good coordination or reflex action should be avoided when the above-mentioned neurological symptoms occur. In most cases, these problems can be avoided by taking the capsules at the recommended times. The 200 mg dosage should be taken at bedtime. The 300 mg dosage should be divided into two doses, 100 mg 2 hours after breakfast and 200 mg at bedtime. (see **DOSAGE AND ADMINISTRATION**, *PROMETRIUM,* **Administration**).

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 (conjugated equine estrogens (CEE), 0.625 mg/day plus medroxyprogesterone acetate (MPA) 2.5 mg/day), 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). [54]

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs. 1.5 cm [0.9], respectively; p=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.[4]

In *the estrogen-alone* arm of the WHI trial (CEE at 0.625 mg/day), 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. [49]

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 with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/ or atypical hyperplasia at breast biopsy). Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of hormone replacement therapy (HRT) 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.

Other doses of conjugated estrogens and medroxyprogesterone acetate and other combinations of estrogens and progestins were not studied in the WHI trial. In the absence of comparable data, these risks should be assumed to be similar.

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

Endometrial hyperplasia and endometrial carcinoma
Estrogen-only HRT increases the risk of endometrial hyperplasia/carcinoma (if taken by women with intact uteri).

There is evidence from several studies that estrogens, unopposed by progestins, increase the risk of carcinoma of the endometrium in humans. However, administration of a progestin for at least the last 12 to 14 days of an estrogen treatment cycle protects the endometrium from hyperplasia and reduces the risk of endometrial hyperplasia/carcinoma cancer to that of untreated women.

Morphological and biochemical studies have shown that 12-14 days of progestin treatment provides maximal control of endometrial mitotic activity. There are possible additional risks, which may be associated with the inclusion of a progestin in estrogen replacement regimens; therefore the manufacturers' labelling should be consulted. The long-term effects generally depend on the dosage and type of progestin used.

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

Cardiovascular
The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[15, 20, 54] 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.[49. 54]

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).[54]

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

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.[49]

HERS and HERS II findings
In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal

women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years. [20]

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD. [15]

Blood Pressure
Women using hormonal replacement therapy (HRT) sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT 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 Phosphorus Metabolism
Because the prolonged use of estrogens, with or without progestins, influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

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

Genitourinary

Vaginal Bleeding
Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt 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 (34 on combined HRT versus 16 on placebo) more cases of venous thromboembolism, including 8 (16 on combined HRT versus 8 on placebo) more cases of pulmonary embolism. [54]

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 (28 on estrogen therapy versus 21 on placebo) more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.[49]

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

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

Jaundice
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Liver Function Test
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.
Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be reevaluated.

Dementia
Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (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. [45, 46]

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo). [46]

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance. [45]

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). [45]

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

Renal

Fluid Retention
Estrogens, 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.

Skin
Contact sensitization
Contact sensitization is known to occur with topical applications. Although it is extremely rare, patients who develop contact sensitization to any component of the gel should be warned that a severe hypersensitivity reaction may occur with continuing exposure to the causative agent.

Special Populations

Pregnant Women:
ESTROGEL® must not be used during pregnancy. Both estrogens and progestins may cause fetal harm when administered to a pregnant woman (see **CONTRAINDICATIONS)**.

If the patient is exposed to PROMETRIUM® (micronized progesterone) capsules during the first 4 months of pregnancy or if she becomes pregnant while taking this drug she should be informed of the potential risks to the fetus.

A case of cleft palate was reported. Additionally rare cases of fetal death (causality not established) have been reported when PROMETRIUM® was used for unapproved indications.

Cases of hepatocellular disease have been reported rarely in women treated with PROMETRIUM® during the second and third trimester (see **ADVERSE REACTIONS**).

Nursing Women:
ESTROGEL® must not be used while breastfeeding (see **CONTRAINDICATIONS)**.

Detectable amounts of progesterone have been identified in the milk of mothers receiving progesterone. The possible effects of progesterone on the nursing infant have not been determined.

Pediatrics: ESTROGEL® should not be used in children.

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

Monitoring and Laboratory Tests

Physical Examination
Before PROMETRIUM® or ESTROGEL® 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, 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.

Adverse events that could be considered to be possibly associated with PROMETRIUM® (micronized progesterone) therapy are: breakthrough bleeding, spotting, and menstrual irregularity.

Under the recommended conditions of use (200 mg HS), dizziness, somnolence, cramps or nausea have been reported occasionally.

Fatigue, headache, vertigo, lightheadedness or migraine have been reported rarely.

Breast:
Breast tenderness may occur with the use of PROMETRIUM®.

Other adverse events which are generally attributed to synthetic progestins and which may possibly occur during PROMETRIUM® treatment include: chloasma, pruritus, jaundice, rash, fluid retention, mental depression and thrombotic disorders.

The following adverse reactions have been reported with estrogen/progestin combinations in general:

- **Blood and Lymphatic System Disorders**
  Altered coagulation tests (see **Warnings and Precautions**, **Drug-Laboratory Test 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

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

ESTROGEL

The following table summarizes the adverse events reported in a single-centre, double-blind, randomized, parallel group, 2 year study (titled "Percutaneous Oestradiol as prophylaxis in early postmenopausal women) designed to examine the efficacy and safety of ESTROGEL® alone or in combination with either micronized progesterone or calcium in the treatment of postmenopausal symptoms as compared to placebo. Fifty-seven (57) patients were randomly divided into four groups and received the following treatment: (1) ESTROGEL® 5g (3 mg E_2) + placebo tablet daily (n=15), (2) ESTROGEL® 5g (3 mg E_2) + 1000 mg oral calcium tablet daily (n=14), (3)

placebo (percutaneous) + 1000 mg oral calcium tablet daily (n=15), (4) placebo (percutaneous and oral) (n=13). After 1 year, patients who were receiving ESTROGEL® were also administered micronized progesterone from day 13 to 24 of each month.

Table 1 – Reported Adverse Events in at least one Patient per Dose Group: Symptoms by Treatment Assignment

Reported Adverse Event	ESTROGEL® n (%)	ESTROGEL®+ Calcium n (%)	Calcium n (%)	Placebo n (%)
Gastrointestinal disorders	1 (6.7%)	2 (14.3%)	5 (33.3%)	2 (15.4%)
Dysfunctional uterine bleeding with vaginal erosion	2 (13.3%)	2 (14.3%)	1 (6.7%)	0
Vulvovaginal dryness	0	0	2 (13.3%)	1 (7.7%)
Hot flushes	0	0	0	1 (7.7%)
Arthralgia	1 (6.7%)	0	0	0
Benign breast neoplasm	0	0	0	1 (7.7%)
Malignant melanoma in the eye	0	0	1 (6.7%)	0
Duodenal ulcer	0	0	0	1 (7.7%)
Anemia	0	0	0	1 (7.7%)
Application site pruritus with erythema	1 (6.7%)	0	1 (6.7%)	0

Twenty one (21) patients reported adverse events summarized in Table 1. Gastrointestinal (GI) discomfort was reported by 10 patients, 2 in the placebo group, 5 in the calcium only group, 1 in the ESTROGEL® only group and 2 in the ESTROGEL® + calcium group. The GI effects were attributed to the calcium supplementation. Two incidents of application site pruritus with erythema were reported: 1 in the ESTROGEL® group (dropped out of the study before 1 month of treatment) and 1 in the calcium group, who reported application site pruritus with erythema for the first 3 to 6 months. Dysfunctional uterine bleeding with vaginal erosion was reported by 4 patients treated with ESTROGEL® or ESTROGEL® + calcium. There were no significant changes in any laboratory parameters.

PROMETRIUM®

Table 2 lists adverse reactions experienced in a double-blind, randomized, parallel-group study that compared the efficacy and safety of PROMETRIUM® 200 mg and 300 mg with placebo for a duration of treatment of 10 days. Two patients withdrew from the study prior to receiving study drug. The majority of adverse reactions experienced are those resulting from the pharmacological action of progesterone as well as from the onset of withdrawal bleeding. These events include cramping, nausea, abdominal pain and/or bloating and tender or swollen breasts.

Table 2: Adverse Reactions Reported in a 60 Patient Double-Blind, Randomized, Parallel-Group Study [Percentage (%) of Patients Reporting]

	PROMETRIUM 200 mg N=19	PROMETRIUM 300 mg N=20	Placebo N=21
Cramps	58%	35%	29%
Nausea	5%	15%	10%
Breast Tenderness	5%	10%	19%
Abdominal Discomfort	5%	10%	14%
Dizziness	11%	15%	14%
Tired/Lethargy	21%	20%	14%

Dupont et al conducted a single-blind, randomized, controlled study that compared percutaneous estradiol and oral conjugated estrogens as replacement therapy (with or without PROMETRIUM®) in sixty-three healthy postmenopausal women for 24 weeks. In this study, serum aldosterone concentrations were slightly elevated in subjects receiving PROMETRIUM® independent of the form of estrogen therapy administered. The increase in aldosterone was not associated with any clinical symptoms or side effects. There was no significant change in diastolic and systolic blood pressure. [10]

Table 3 lists adverse experiences which were reported in ≥2% of patients (regardless of relationship to treatment) who received cyclic PROMETRIUM® Capsules, 200 mg daily (12

days per calendar month cycle) with daily 0.625 mg conjugated estrogen, in a multicenter, randomized, double-blind, placebo-controlled clinical trial (Postmenopausal Estrogen and Progestin Interventions (PEPI) Trial) in 875 postmenopausal women. Table 3 also lists adverse experiences reported in the conjugated estrogen-alone group and placebo group of the PEPI trial.

Table 3 : Adverse Experiences (≥2%) Reported in an 875 Patient Placebo-Controlled Trial in Postmenopausal Women over a 3-Year Period [Percentage (%) of Patients Reporting]

	PROMETRIUM® Capsules 200 mg with Conjugated Estrogens 0.625 mg	**Conjugated Estrogens 0.625 mg (only)**	**Placebo**
	(N=178)	**(N=175)**	**(N=174)**
Headache	31	30	27
Breast Tenderness	27	16	6
Joint Pain	20	22	29
Depression	19	18	12
Dizziness	15	5	9
Abdominal Bloating	12	10	5
Hot Flashes	11	14	35
Urinary Problems	11	10	9
Abdominal Pain	10	13	10
Vaginal Discharge	10	10	3
Nausea / Vomiting	8	6	7
Worry	8	5	4
Chest Pain	7	4	5
Diarrhea	7	7	4
Night Sweats	7	5	17
Breast Pain	6	6	2
Swelling of Hands and Feet	6	9	9
Vaginal Dryness	6	8	10
Constipation	3	3	2

Post-Market Adverse Drug Reactions

During the marketing of PROMETRIUM® internationally, cases of hepatocellular liver disease have been reported rarely. Most of these occurred in women treated outside of the approved indications, i. e., during the second and third trimester of pregnancy when premature labour was threatened.

Additional adverse experiences have been observed in women taking progestins in general: anaphylaxis and anaphylactoid reaction, rash with and without pruritus, confusion, speech disorder, impaired concentration, and hot flashes. Additionally, rare instances of syncope have been reported.

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

DRUG INTERACTIONS

Overview

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Drugs Inducing Liver Enzymes: Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampin) may interfere with the activity of orally administered progestins and orally administered estrogens.

Drugs Inhibiting Liver Enzymes: Metabolism of progesterone capsules by human liver microsomes was inhibited by ketoconazole (IC_{50} <0.1 microM; ketoconazole is a known inhibitor of cytochrome P450 3A4). These data therefore suggest that ketoconazole may increase the bioavailability of progesterone. The clinical relevance of the in vitro findings is unknown.

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

Concomitant administration of aminoglutethimide with MPA may significantly reduce the bioavailability of MPA. It is unknown whether this interaction occurs with micronized progesterone.

Drug-Drug Interactions

The following section contains information on drug interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) that have been reported in the public literature (Tables 4 & 5). It is unknown whether such interactions occur with drug products containing other types of estrogens.

Therapeutic monitoring is recommended.

Table 4 - Drugs Which May Affect the Concentrations of Ethinyl Estradiol

Drug	Ref	Proposed Mechanism	Effect
Acetaminophen	Literature		Increased AUC and/or plasma concentrations of ethinyl estradiol
Anticonvulsants Phenobarbital Phenytoin Carbamazepine	Literature	Increased metabolism of ethinyl estradiol	Decreased plasma concentrations of estradiol
Ascorbic acid	Literature		Increased AUC and/or plasma concentrations of ethinyl estradiol
Atorvastatin	Literature		When co-administered with certain ethinyl estradiol containing drug products (e.g. oral contraceptives containing ethinyl estradiol), the AUC values of ethinyl estradiol increase by 20 percent.
Rifampin	Literature	Increased metabolism of ethinyl estradiol	Decreased plasma concentrations of estradiol. Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.
Troglitazone	Literature		When co-administered with certain ethinyl estradiol containing drug products (e.g. oral contraceptives containing ethinyl estradiol), the plasma concentrations of ethinyl estradiol reduce by 30 percent.

Table 5 - Modification of Other Drug Action by Co-administration with Certain Drugs Containing Ethinyl Estradiol (e.g. oral contraceptives containing ethinyl estradiol)

Drug	Ref	Effect
Acetaminophen	Literature	Decreased plasma concentrations of acetaminophen
Clofibric Acid	Literature	Increased clearance of clofibric acid
Cyclosporin	Literature	Increased plasma concentrations of cyclosporine
Morphine	Literature	Increased clearance of morphine
Prednisolone	Literature	Increased plasma concentrations of prednisolone
Salicylic Acid	Literature	Increased clearance of salicylic acid
Temazepam	Literature	Increased clearance of temazepam
Theophylline	Literature	Increased plasma concentrations of theophylline

Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds or induce the conjugation of other compounds.

Drug-Food Interactions

Concomitant food ingestion increased the AUC and Cmax values of PROMETRIUM® Capsules, with no effect on Tmax relative to a fasting state when administered to postmenopausal women at a dose of 200mg, for information see ACTION AND CLINICAL PHARMACOLOGY / Pharmacokinetics.

Interaction of ESTROGEL® with food has not been established.

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.

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

ESTROGEL®

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

• increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;

• increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T4) as measured by column or radioimmunoassay;T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered;

• other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;

- impaired glucose tolerance;
- increased serum triglycerides and phospholipids concentration.

Administration of ESTROGEL®, alone or in combination with oral micronized progesterone has no effect on antithrombin III. Postmenopausal women treated with ESTROGEL® and oral micronized progesterone for three months showed no significant variations in platelet count, thromboelastinogram, factors II, VII, IX, X, prothrombin time, fibrinogen, antithrombin III and plasminogen. No shift towards hypercoagulability was observed. A moderate decrease in platelet aggregation was observed without any related clinical symptoms. In combination with oral micronized progesterone, ESTROGEL® does not negatively affect the balance between the vasoactive prostanoids PGI2 and TxA2.

A study has shown that transdermal estradiol improves the anticoagulant response to activated protein C (APC-sensitivity), probably as a result of a decreased factor VIII.

Clinical trials demonstrated no increase of SHBG with percutaneous estradiol or increase to a lesser extent compared to oral conjugated estrogens.

Based on a study, transdermal estradiol did not significantly increase circulating levels of TBG and CBG.

PROMETRIUM®

The following laboratory results may be altered by the use of progesterone:
levels of gonadotropin, plasma progesterone, and urinary pregnanediol.
The results of certain endocrine and liver function tests may be affected by progestin-containing products:

- impaired glucose tolerance;
- reduced serum folate concentration;
- change in plasma lipoprotein levels.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks. The pathologist should be informed that the patient is receiving HRT therapy when relevant specimens are submitted.

Drug-Lifestyle Interactions
Acute alcohol ingestion during HRT may lead to elevations in circulating estradiol levels.

DOSAGE AND ADMINISTRATION

ESTROGEL®

Dosing Considerations
Because of the variable absorption of ESTROGEL® between individuals due to the technique of self administration on the skin, it is recommended to obtain measurement of serum estradiol level after initiation of treatment. This measurement should be done when the patient has developed her technique for ESTROGEL® application when she comes for her regular follow-up visit. This measurement should be similar to the serum estradiol level normally produced by the ovary before menopause during the middle part of the follicular phase of the menstrual cycle (150-400 pmol/L).

In women who are not currently taking oral estrogens, treatment with ESTROGEL® can be initiated at once. In women who are currently taking oral estrogen, treatment with ESTROGEL®

can be initiated 1 week after withdrawal of oral therapy or sooner if symptoms reappear before the week's end.

In women with intact uteri, a progestin should be sequentially co-administered for a minimum of 12-14 days each cycle to prevent endometrial hyperplasia.

Continuous, non-cyclic therapy may be indicated in hysterectomized women or in cases where the signs and symptoms of estrogen deficiency become problematic during the treatment-free interval.

There have been no reported cases of biologically significant estradiol transfer from a patient using ESTROGEL® to their male partner.

Recommended Dose and Dosage Adjustment

Treatment is usually initiated with 2.5 g ESTROGEL®, daily. ESTROGEL® is usually administered on a cyclic schedule from day 1 to day 25 of each calendar month or from day 1 to day 21 of a 28-day cycle.

The dose of ESTROGEL® should be adjusted as necessary to control symptoms. Attempts to adjust the necessary dosage should be made after two months of treatment. Breast discomfort and/or breakthrough bleeding are generally signs that the dose is too high and needs to be lowered. However, if the selected dose fails to eliminate the signs and symptoms of estrogen deficiency, a higher dose may be prescribed. For maintenance therapy, the lowest effective dose should be used.

Missed Dose

If a dose of ESTROGEL® has been missed, the missed dose should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule should be continued. The dose of ESTROGEL® should not be doubled.

Administration

ESTROGEL® Metered-Dose Pump

Two metered-actuations will deliver 2.5 g of gel (1.5 mg E_2). All of the gel should be applied with the hands over a large area of skin (>2000 cm2) in a thin, uniform layer.

To measure a 2.5 g dose of ESTROGEL® (1.5 mg E_2), press firmly on the pump once and apply the gel to one arm. Repeat applying the gel to the opposite arm. It is recommended to apply ESTROGEL® to both arms. Alternate sites of application are the abdomen or the inner thighs. It is not necessary to rotate the site of administration. **ESTROGEL® must not be applied to the breasts**. ESTROGEL® must not be applied to the face or to irritated or damaged skin. Allow the gel to dry approximately 2 minutes before covering with clothing. ESTROGEL® does not stain or smell.

When a new metered-dose pump is opened, it may be necessary to prime the pump by pressing the pump once or twice. The first metered-actuation may not be accurate and should therefore be discarded. The pump contains enough gel for approximately a month's use (i.e. 64 metered-

actuations). After that, the amount of gel delivered may be lower and thus, it is recommended to change the pump.

ESTROGEL® 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.

PROMETRIUM®

Recommended Dose and Dosage Adjustment

Hormone Replacement Therapy: In general, the dosage of PROMETRIUM® (micronized progesterone) is 200 mg daily for the last 14 days of estrogen treatment per cycle (i.e. from day 8 to day 21 for a 28-day cycle, and from day 12 to day 25 for a 30-day cycle). Estrogens should be administered daily at the lowest effective dose. Patients being treated with high dosages of estrogen (equivalent to 1.25 mg conjugated estrogens or higher) should be administered 300 mg daily for the last 12-14 days of estrogen treatment.

The dosage of PROMETRIUM® should be proportional to the dosage of estrogen. With adequate adjustment of the dosage of PROMETRIUM®, patients should experience either regular withdrawal uterine bleeding or cessation of bleeding (amenorrhea).

Missed Dose

If a patient is treated with 200 mg daily (total dose at bedtime) and she forgets to take this dose, she should take an extra dose of one capsule (100 mg) the following morning and continue taking the rest of the capsules as prescribed. If a patient is treated with 300 mg daily, and she forgets to take a morning or evening dose, she should not take the missed dose.

Administration

The 200 mg daily dosage of PROMETRIUM® should be taken at bedtime. Patients receiving 300 mg PROMETRIUM® daily should take one capsule (100 mg) in the morning and two capsules (200 mg) at bedtime. The morning dose should be taken 2 hours after breakfast.

OVERDOSAGE

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

ESTROGEL®

Symptoms

Numerous reports of the ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, abdominal cramps, headache, dizziness, bloating or vaginal bleeding in women.

ESTROGEL® does not contain progestins. However, in the case where a progestin is co-administered, progestin (norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

Treatment
Symptomatic treatment should be given.

PROMETRIUM®

Symptoms
The toxicity of progesterone is very low. Symptoms that may occur are: nausea, vomiting, somnolence and dizziness.

Progestin (norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

ACTION AND CLINICAL PHARMACOLOGY

ESTROGEL®

Mechanism of Action
ESTROGEL® is a transdermal preparation which is comprised of a hydro-alcoholic gel containing 0.06% of the physiological hormone, 17ß-estradiol (E_2).

Pharmacodynamics
Treatment of postmenopausal women with ESTROGEL® provides swift and effective relief from climacteric symptoms such as hot flushes, vaginal atrophy and insomnia. Co-administration of a progestin does not affect the efficacy of ESTROGEL® to relieve climacteric symptoms and has been shown to be an effective method to prevent estrogen-induced endometrial hyperplasia.

In general, administration of ESTROGEL®, in combination with a progesterone substitute, does not lead to significant changes in systolic and diastolic blood pressure or heart rate in normotensive women. In only one open study, examining normotensive and hypertensive women, was a slight but significant reduction in blood pressure (remaining within the normal range) observed after 3 years of treatment. Administration of ESTROGEL® does not lead to any significant change in rennin substrate, even when administered to diabetic patients.

Administration of ESTROGEL® has no significant effect on carbohydrate metabolism, even when administered to non-insulin dependent diabetics.

Pharmacokinetics
Percutaneous administration of ESTROGEL® produces plasma concentrations of estradiol and estrone that are similar to those observed in the follicular phase of the ovulary cycle.

Absorption:
Following application to human skin, ESTROGEL® rapidly penetrates the stratum corneum and then diffuses more slowly into the epidermis, dermis and vascular system over several hours. When ESTROGEL® is applied on skin, it dries in 2 to 5 minutes.

ESTROGEL® 2.5 g was administered to 17 postmenopausal women once daily on the posterior surface of one arm from wrist to shoulder for 14 consecutive days.

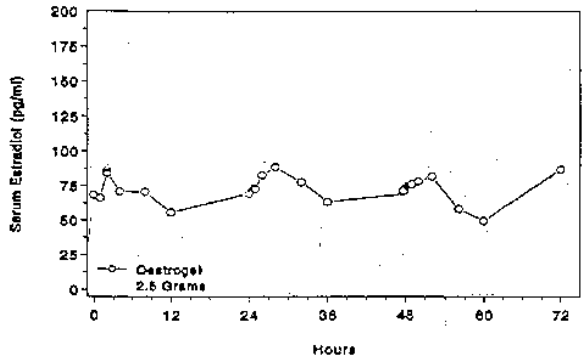
Maximal serum concentrations of estradiol and estrone on day 12 were 117 pg/mL and 128 pg/mL, respectively. The time-averaged serum estradiol and estrone concentration over the 24-hour dose interval after administration of 2.5 g ESTROGEL® on Day 12 are 76.8 pg/mL and 95.7 pg/mL, respectively.

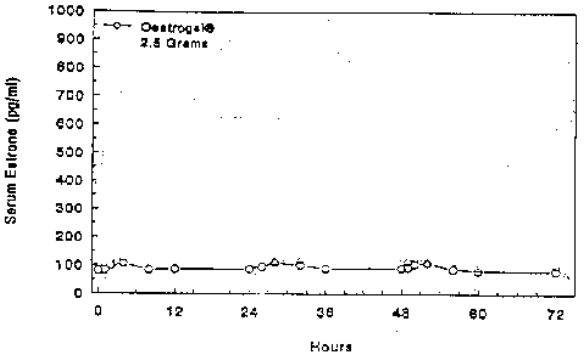
Day	Parameter	Estradiol	Estrone	Estradiol/Estrone ratio
11	**Cmax**	114 pg/mL (44) (417 pmoles/L)	128 pg/mL (57) (473 pmoles/L)	1.02 (42) -
	Tmax	9.50 (102)	7.83 (106)	0.85 (42)
	AUC (0-24hr)	1745 (40)	2343 (56)	-
	Cavg	72.2 pg/mL (39) (264 pmoles/L)	92.8 pg/mL (57) (343 pmoles/L)	
12	**Cmax**	117 pg/mL (42) (428 pmoles /L)	128 pg/mL (57) (473 pmoles /L)	1.09 (55) -
	Tmax	6.75 (126)	12.7 (70)	0.81 (38)
	AUC (0-24hr)	1684 (37)	2326 (54)	-
	Cavg	76.8 pg/mL (30) (281 pmoles/L)	95.7 pg/mL (53) (354 pmoles /L)	
13	**Cmax**	117 pg/mL (51) (428 pmoles /L)	123 pg/mL (63) (455 pmoles/L)	1.08 (35) -
	Tmax	7.92 (124)	6.50 (111)	0.81 (33)
	AUC (0-24hr)	1624 (55)	2142 (62)	-
	Cavg	70.7 pg/mL (50) (259 pmoles/L)	88.3 pg/mL (60) (326 pmoles/L)	

Cmax maximum serum concentration (pg/mL)
Tmax time of maximum serum concentration (hr)
AUC (0-24hr) area under the serum concentration-time curve from time zero to 24 hr
Cavg average serum concentration (pg/mL)

Mean concentrations-time profiles for estradiol and estrone are shown in Figures 1 and 2.

Figures 1 & 2 - Serum Concentration Time Curves of estradiol and estrone on Days 11-13 Following Multiple Administration of ESTROGEL® 2.5 g to Postmenopausal Women





Daily percutaneous administration of ESTROGEL® results in increasing plasma estradiol levels, which plateau after 4-5 days of treatment, remaining relatively stable thereafter.

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 blood largely bound to sex hormone binding globulin (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 the major urinary metabolite. Estrogens also undergo enterohepatic

recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant 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 ESTROGEL® does not go through the first pass liver metabolism.

Excretion:
Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

PROMETRIUM®

Mechanism of Action
PROMETRIUM® (micronized progesterone) is an oral dosage form of the naturally occurring steroid; it is chemically identical to progesterone of ovarian origin.

Progestins are used in combination with estrogens to prevent estrogen-induced endometrial hyperplasia and reduce the risk of endometrial carcinoma to that of untreated women.

Clinical Pharmacology
PROMETRIUM® is intended for use in women with an intact uterus as an adjunct to estrogen replacement therapy. Progesterone exerts significant anti-proliferative effects on the estrogenized endometrium and maintains sufficient control of endometrial mitotic activity through suppression of nuclear estradiol receptors, significant reduction in epithelial and stromal DNA synthesis and induction of 17ß-estradiol dehydrogenase and isocitric dehydrogenase activity.

PROMETRIUM® administered per os is a physiologic inhibitor of aldosterone and thus increases the sodium excretion rate. A 200 mg dose of micronized progesterone is equivalent to a dose of 25 to 50 mg of spironolactone as an aldosterone inhibitor.

PROMETRIUM® has no significant effect on carbohydrate metabolism, even when administered to non-insulin dependent diabetics. PROMETRIUM® does not negate the beneficial oral or transdermal estrogen-induced effect on lipoprotein profiles. In general, administration of PROMETRIUM® (with or without estrogen) does not lead to significant changes in systolic and diastolic blood pressure or heart rate in normotensive women. Administration of PROMETRIUM® does not lead to any significant change in renin substrate, even when administered to diabetic patients. Administration of PROMETRIUM® in combination with percutaneous estradiol produces a decrease in blood platelet aggregation in perimenopausal women. In combination with oral conjugated estrogens, PROMETRIUM® does not negatively affect the balance between the vasoactive prostanoids PGI_2 and TxA_2.

Pharmacokinetics

Absorption and Distribution

Pharmacokinetic studies indicate that plasma progesterone levels within the luteal range are achieved with peak levels (mean 77.3 nmol/L) at 2-4 hours following oral administration to postmenopausal women of PROMETRIUM® 200 mg.

Table 6: Mean Pharmacokinetic parameters in postmenopausal women after five daily doses of PROMETRIUM® capsules.

Mean (n=15) Day 5 Progesterone Cmax and AUC Values after Administration of PROMETRIUM 200 and 300 mg Once-Daily		
	PROMETRIUM Dose (mg/day)	
	200	300
Cmax (nmol/L)	121.2	192.7
AUC_{0-10} (nmol•hr/L)	321.8	558.7

The plasma concentration of progesterone then declines slowly but remains within the range found in the mid-luteal phase for approximately 9 to 12 hours after administration. Plasma progesterone levels remain above baseline 84 hours after administration of the final dosage. Ingestion of food following administration of PROMETRIUM® significantly increases AUC and Cmax values, with no effect on Tmax. Bioavailability (defined as area under the curve, AUC) is linearly related to the dose.

Progesterone concentrations measured in the endometrium after 8 days of treatment with PROMETRIUM® either 200 mg/day or 300 mg/day are comparable to physiologic levels during the luteal phase even 12 hours after administration. This fact demonstrates the strong retention of this hormone in target tissue, which is responsible for its biological action during 24 hours. Similarly, significant increases in progesterone concentrations occur in breast tissue.

Intestinal absorption is rapid. Micronization of progesterone improves its absorption by the digestive tract by increasing the surface area in contact between the steroid and the mucous membrane.

Metabolism and Excretion

Following administration of PROMETRIUM® 300 mg, the major inactive metabolite (pregnanediol-3 α glucuronide) and the 2 major active metabolites (17-hydroxyprogesterone, 20 α dihydroprogesterone) show similar plasma profiles to progesterone. Twenty-four hours following oral administration of 200 mg of PROMETRIUM® to postmenopausal women, 22.8 mg of pregnanediol glucuronide are eliminated in urine. The second major excretion pathway is via the bile and the feces.

Since PROMETRIUM® is metabolized primarily by the liver and is excreted mainly in the urine, patients with illness related to the liver and/or kidneys should be monitored closely.

Special Populations and Conditions

Geriatrics (> 65 years of age):

No clinical studies were conducted to evaluate the effect of ESTROGEL® on women more than 65 years old.

Pediatrics:

ESTROGEL® should not be used in children.

Gender:

ESTROGEL® should be used in women only.

Estrogen pharmacology

With daily administration of 2.5 g or 5 g ESTROGEL® (corresponding to 1.5 mg or 3 mg estradiol, respectively), mean serum estradiol concentrations of approximately 80 pg/ml (294 pmol/L) and 150 pg/ml (551 pmol/L), respectively, are maintained. Administration of ESTROGEL® also results in increased serum estrone concentrations, producing a physiological estradiol/estrone ratio of approximately one. Therefore, serum concentrations of both estradiol and estrone and the serum estradiol/estrone ratio provided by ESTROGEL® are consistent with physiological levels observed during the follicular phase of the normal menstrual cycle.

Estrogen exerts a dose-dependent stimulating effect on mitosis (proliferation) of the endometrium. Unopposed estrogen increases the risk of endometrial hyperplasia/carcinoma. Therefore, ESTROGEL® should be prescribed with an appropriate dosage of progestin for women with intact uteri.

STORAGE AND STABILITY

Store at controlled room temperature 15°-30°C. Protect from light.

Keep in a safe place out of the reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS

See **DOSAGE AND ADMINISTRATION - Administration** section for ESTROGEL®.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ESTROGEL PROPAK™ (17ß-estradiol and micronized progesterone) is available in a carton containing one ESTROGEL® (17ß-estradiol) 80 g metered-dose pump and one blister pack of 30 PROMETRIUM® (micronized progesterone) 100 mg capsules.

ESTROGEL®

ESTROGEL® contains 0.06% 17ß-estradiol as hemihydrate in a specially formulated hydro-alcoholic gel to provide a sustained absorption of the active ingredient. ESTROGEL® is packaged in 80 g metered-dose pumps. Each metered-actuation delivers 1.25 g of Gel (0.75 mg of 17β-estradiol). Non-medicinal ingredients are Carbopol 980, triethanolamine, ethanol and purified water.

PROMETRIUM®

PROMETRIUM® (micronized progesterone) 100 mg capsules to be taken orally; contain 100 mg micronized progesterone as the active ingredient. PROMETRIUM® 100 mg progesterone capsules are available in unit dose blister packages, with 30 capsules per package. PROMETRIUM® 100 mg capsule is a round, opaque, off-white to slightly yellow, shiny, soft gelatin capsule. Medicinal ingredient: each capsule contains 100 mg micronized progesterone. Non-medicinal ingredients: sunflower oil, gelatin, glycerin, soya lecithin (may contain traces of medium chain triglycerides), titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

ESTROGEL®

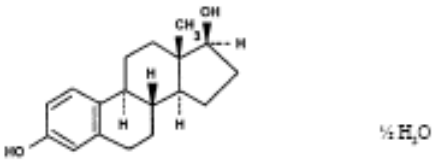
Proper name: 17β-estradiol (as estradiol hemihydrate)

Chemical name: estra-1,3,5(10)-triene-3,17ß-diol hemihydrate

Molecular formula: 281.4

Molecular mass: $C_{18}H_{24}O_2$, ½ H_2O

Structural formula:



Physicochemical properties:

Physical form: White or creamy white, odourless, crystalline powder

Solubility: Practically insoluble in water; sparingly soluble in vegetable oils; soluble in alcohol, acetone, dioxane, chloroform and in solutions of fixed alkali hydroxides.

Melting range: 173°C - 179°C

PROMETRIUM®

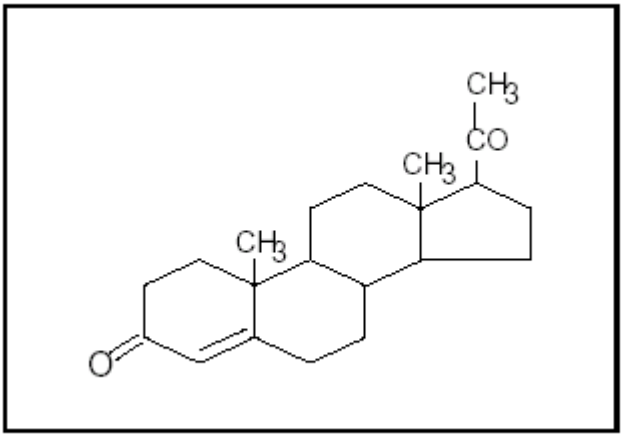
Proper name: Progesterone, U.S.P. micronized

Chemical name: Pregn-4-ene-3,20-dione

Molecular formula: $C_{21}H_{30}O_2$

Molecular mass: 314.47

Structural formula:



Physicochemical properties:

Physical form: White or creamy white, odourless, crystalline powder.

Solubility: Practically insoluble in water; soluble in acetone and in dioxane; one gram dissolves in about 0.3 mL of chloroform, in about 8 mL of alcohol and in about 16 mL of ether; sparingly soluble in vegetable oils.

Melting range: 126°C - 131°C.

CLINICAL TRIALS

ESTROGEL®

Efficacy and Safety Studies
Study demographics and trial design

Table 7 – Summary of patient demographics for 17ß-estradiol clinical trials in hormone replacement therapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects number	Age range	Gender
Dupont Study	Single-blind, randomized, active treatment, controlled study	A:17β-estradiol (2.5 g/day, percutaneous) B: oral conjugated estrogens; (0.625 mg/day, oral) The dose of 17β-estradiol and oral conjugated estrogens was adjusted during the 1st 3 cycles according to clinical symptomatology. Treatment was administered on days 1-25 of a 28-day cycle over 6 months. 200 mg micronized progesterone given orally on days 12-25 (in non-hysterectomized subjects)	A: 32 [a] B: 31 [b]	A: 37-59 B: 34-60	Female
March Study	Single center, double-blind, placebo-controlled, randomized study	A: 17β-estradiol (2.5 g/day, percutaneous); B: Placebo gel (percutaneous) Treatment provided 3 weeks per month for a period of 3 months	A: 22 B: 22	48-50	Female
Christiansen Study	Single-centre, double-blind, randomized, parallel group , controlled study	A: 17β-estradiol (5g/day; percutaneous) + placebo tablet (daily) B: 17β-estradiol (5g/day; percutaneous) + calcium tablet (1000 mg/day) C: Calcium tablet (1000 mg/day) + placebo (percutaneous) D: Placebo (percutaneous and oral) 17β-estradiol/placebo percutaneous administered on days 1-24 of 28 day cycle. Progesterone was provided open label to subjects receiving 17β-estradiol (A, B) after the first year from day 13-24 of each month.	A: 15 B:14 C:15 D:13	49-51	Female

[a] 16 hysterectomized postmenopausal women; 16 non-hysterectomized postmenopausal women
[b] 15 hysterectomized postmenopausal women; 16 non-hysterectomized postmenopausal women

Pivotal Clinical Trials

Dupont Study

A single-blind, randomized, controlled study compared the effectiveness of 17ß-estradiol to that of oral conjugated estrogens, given either with or without oral micronized progesterone, as hormone replacement therapy (HRT) for menopause over a period of 6 months. Criteria of effectiveness were determined by monitoring climacteric symptoms, transformation of the endometrium and endocrine profiles. Sixty-three healthy postmenopausal women entered the study. 17ß-estradiol (2.5 g) or oral conjugated estrogens (0.625 mg) was administered daily to hysterectomized (31 women, 16 receiving 17ß-estradiol) and non-hysterectomized (32 women, 16 receiving 17ß-estradiol) women from day 1 to day 25 of a 28-day cycle. Non-hysterectomized women also received 200 mg oral micronized progesterone on day 12 to day 25 of the 28-day cycle. No patients dropped-out during this study. The dosage of 17ß-estradiol and oral conjugated estrogens was adjusted during the first three cycles according to clinical symptomatology.

17ß-estradiol (2.5 g) with or without progesterone relieved climacteric symptoms in 56% of the women. Oral conjugated estrogens (0.625 mg) with or without progesterone provided symptomatic relief in 56% and 40% of patients, respectively. After the first cycle, 17ß-estradiol was adjusted to 3.75 g for 34% of the women, while 24% of the women required an increase of oral conjugated estrogens to 0.9 mg. At the beginning of the third cycle, the dosage of 17ß-estradiol was increased to 5 g in 9% of women, while the dose of oral conjugated estrogens was increased to 1.25 mg in 26% of women to further reduce or eliminate hot flushes and improve insomnia/night sweats (Figure 3).

Both 17ß-estradiol and oral conjugated estrogens, with or without micronized progesterone, improved hot flushes and insomnia/night sweats. The percentage of patients showing improvement increased over the first 3 cycles with titration of the estrogen dose (Figure 3). Improvement of asthenia was greater with the combination of 17ß-estradiol and micronized progesterone at the 2^{nd} cycle of treatment ($p=0.01$). No difference was found between groups for cycles 1, 3 and 6 (Figure 4). Of the women diagnosed with severe or moderate atrophy of vaginal mucosa prior to treatment, the vaginal mucosa became normal in 80% (8/10), 100% (5/5), 93% (13/14) and 73% (11/15) of cases at the end of the sixth cycle of 17ß-estradiol alone, oral conjugated estrogens alone, 17ß-estradiol + micronized progesterone and oral conjugated estrogens + micronized progesterone treatments, respectively (Figure 5). Both 17ß-estradiol and oral conjugated estrogens provided relief from climacteric and atrophic urogenital symptoms. Administration of 17ß-estradiol produced serum 17-estradiol (E_2) and estrone (E_1) levels within those expected for the premenopausal range. The E_2/E_1 ratio for the 17ß-estradiol patients was approximately equal to the physiologic norm of one (1.192), but was much lower in the oral conjugated estrogens group (0.137). Serum levels of FSH and LH were lowered with both estrogenic preparations but remained above the premenopausal range. Addition of micronized progesterone increased the inhibitory effect of 17ß-estradiol and oral conjugated estrogens on both LH and FSH. No change in the concentration of angiotensinogen was noted for 17ß-estradiol patients, while a 2.5 fold increase was observed in women receiving oral conjugated estrogens with or without progesterone. Patients receiving oral micronized progesterone with either estrogen preparation showed an increase in aldosterone. No clinical symptoms or side-effects were found to be associated with the increases in aldosterone and angiotensinogen

including no significative change of diastolic and systolic blood pressure or body weight. Mitotic activity remained low in all cases after three or more days of micronized progesterone treatment, and no patients showed cystic or glandular hyperplasia. The anti-proliferative endometrial control seen in patients receiving 200 mg micronized progesterone in addition to either 17ß-estradiol or oral conjugated estrogens appeared sufficient in all patients. Most of the patients (47%) remained amenorrheic and 34% had regular withdrawal bleeding. The present data indicate that 17ß-estradiol in combination with oral micronized progesterone provides efficient relief of climacteric and urogenital symptoms without exerting any effect on hepatic function while maintaining the ratio of serum E_2/E_1 at the physiological level of 1.0.

Figure 3 - Percentage of improvement of hot flushes and improvement of sleep during the first three cycles of replacement therapy

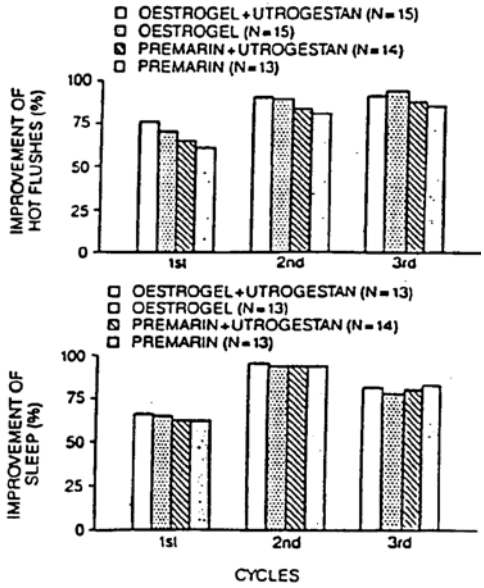


Figure 4 - Percentage of improvement of asthenia (cycles 1 through 6)

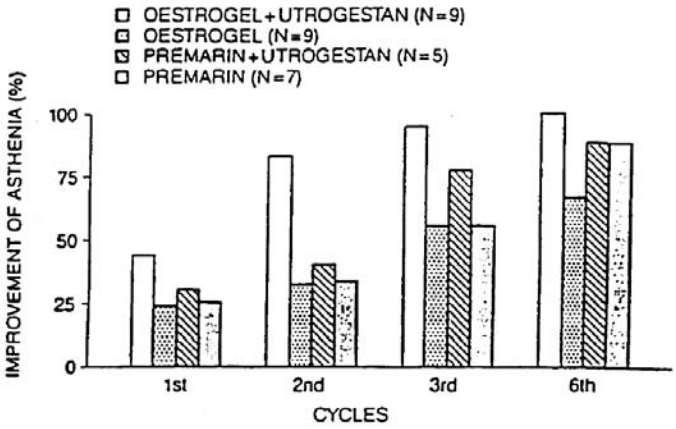
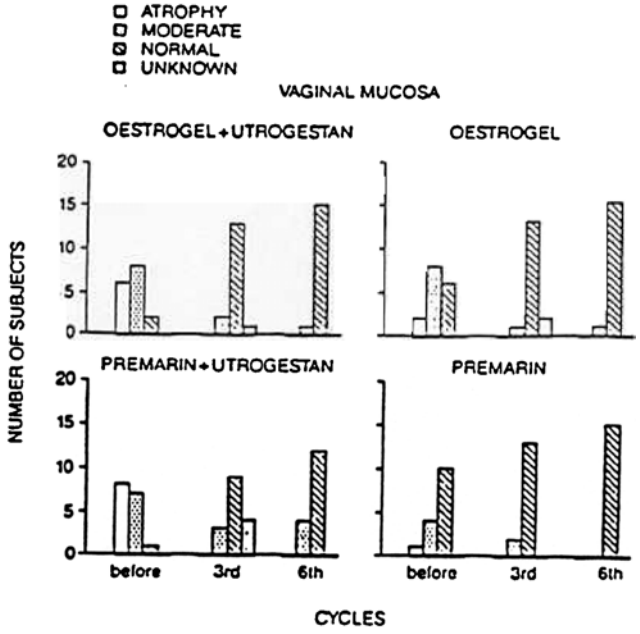


Figure 5 - Effect of HRT on vaginal mucosa



March Study

Another double-blind, randomized, placebo-controlled study compared the efficacy and safety of 17ß-estradiol (2.5 g) and placebo in the treatment of moderate to severe menopausal symptoms. The protocol was designed as a 14-week study, with a 2-week run-in period, and a 12-week double-blind treatment period, during which patients received either 17ß-estradiol or placebo gel. Of the forty-four patients which were randomized into the study, 22 received 2.5 g of 17ß-estradiol 3 weeks/month, for a period of 3 months and 22 received placebo. Eight patients did not complete the study or could not be evaluated for efficacy.

Patients treated with 17ß-estradiol showed a statistically significantly greater response in the improvement of vasomotor symptoms than patients receiving placebo. Following 3 months of treatment, 95% of patients receiving 17ß-estradiol showed improvement in the severity of their vasomotor symptoms as compared to 39% of patients receiving placebo. Patients treated with 17ß-estradiol showed a statistically significant improvement in the frequency of vasomotor attacks as compared to patients treated with placebo. Sixty five to 85% of patients treated with 17ß-estradiol showed fewer episodes of hot flushes as compared to 30% of patients treated with placebo. Hormonal activity (as seen on vaginal cytology) and estradiol levels were statistically significantly increased in patients receiving 17ß-estradiol as compared to patients receiving placebo. FSH levels were significantly decreased in patients treated with 17ß-estradiol as compared to patients treated with placebo.

The reported adverse reactions were mild to moderate in severity and were consistent with side effects experienced with estrogen replacement therapy. Sixteen (16) patients experienced adverse reactions, 6 of which were receiving 17ß-estradiol. Patients treated with 17ß-estradiol reported slightly more adverse events as compared to patients treated with placebo.

Christiansen Study
A third double-blind, randomized, parallel group study evaluated the efficacy and safety of 17ß-estradiol alone or in combination with calcium, with or without micronized progesterone, in the treatment of postmenopausal symptoms as compared to treatment of calcium alone or placebo.

Of the fifty-seven (57) patients who participated in the 2-year study, twenty nine (29) patients received 17ß-estradiol. During the second year, open label progesterone was added to the 17ß-estradiol groups. Efficacy and safety were evaluated through symptoms of menopause, using the Kupperman index, and laboratory parameters. Twelve (12) patients prematurely terminated the study, 9 of which were receiving 17ß-estradiol.

The 17ß-estradiol groups showed significant improvement in symptoms of menopause. Hot flushes, insomnia and nervousness were affected by 17ß-estradiol. With respect to severity of vasomotor symptoms, treatment differences at each visit were statistically significant (except at 15 months). Patients in both placebo and calcium groups had at least a 70% chance of having more symptoms than those in the 17ß-estradiol groups. The addition of oral progesterone to the 17ß-estradiol groups at 12 months did not appear to have any effect on the menopausal symptomatology.

The main adverse reaction reported was GI discomfort due to the calcium supplementation. Two cases of application site pruritus with erythema were reported.

The study shows that 17ß-estradiol is effective and safe in the treatment of menopausal symptoms.

PROMETRIUM®

A long-term study evaluated the efficacy and safety of PROMETRIUM® (micronized progesterone) 200 mg and 300 mg to prevent endometrial hyperplasia in postmenopausal women receiving long term Hormone Replacement Therapy (HRT). The study also aimed to identify those characteristics of endometrial morphology that are essential for long term safety in postmenopausal women who are receiving different combinations of estradiol and progesterone over a period of five or more years. Two hundred thirty six (236) women having natural symptomatic menopause and seeking hormone replacement therapy were initiated into the study.

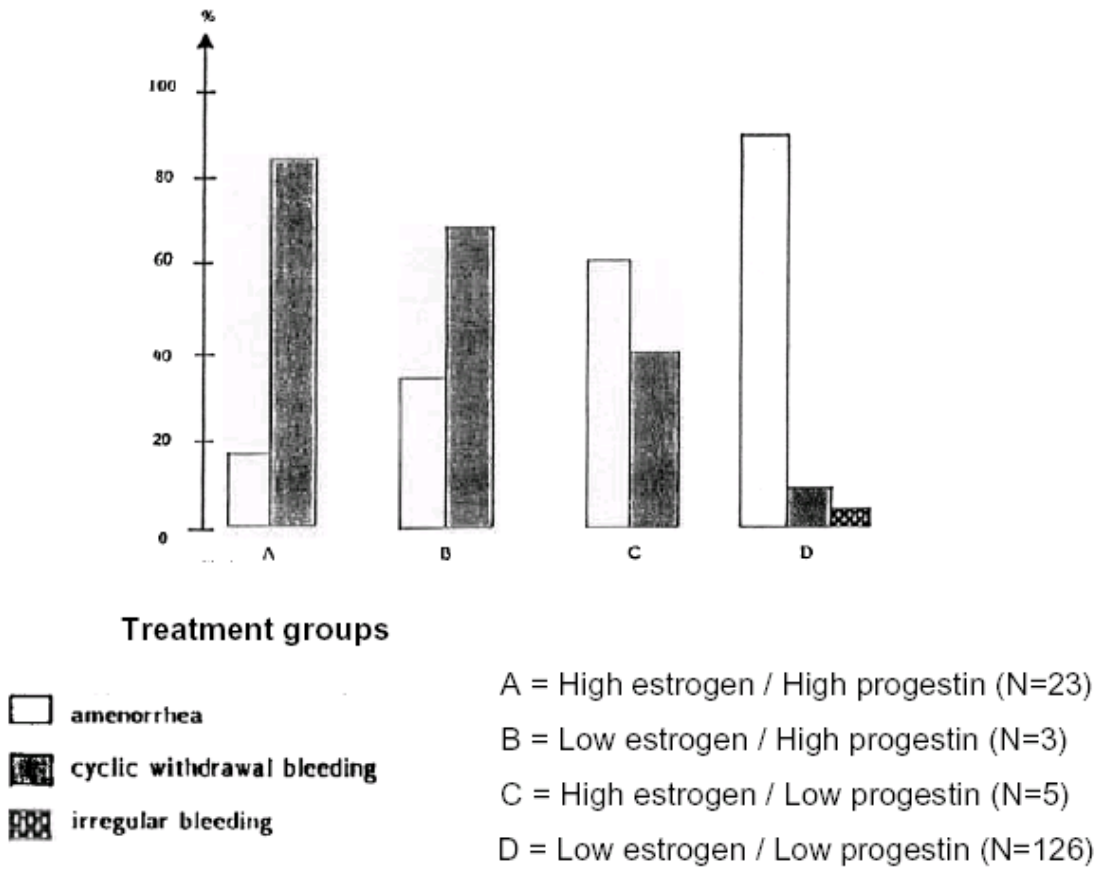
The women were treated with an initial low dose of 1.5 mg percutaneous estradiol, for 21 days out of 28, and 200 mg oral micronized progesterone, given for the last 14 days of estrogen treatment. Within the first 6 months of treatment, the initial progesterone dose was eventually increased to 300 mg in patients willing to have regular withdrawal bleeding and who did not have it with 200 mg per day. The monthly duration of estradiol treatment was prolonged to 25 days out of 28 in the case of recurrence of clinical symptoms during the treatment free week and the monthly duration of oral micronized progesterone treatment was shortened to 10 or 12 days in the case of early uterine bleeding appearing before the end of the course of each cycle of treatment. The 200 mg PROMETRIUM® dose was given at bedtime. The 300 mg dose was divided into 100 mg taken in the morning and 200 mg at bedtime. The treatment groups were as follow: 126 women received 1.5 mg estradiol plus 200 mg micronized progesterone (Treatment

Group A), 3 women received 1.5 mg estradiol plus 300 mg micronized progesterone (Treatment Group B), 5 women received 3 mg estradiol plus 200 mg micronized progesterone (Treatment Group C) and 23 women received 3 mg estradiol plus 300 mg micronized progesterone (Treatment Group D).

Of the 236 women initiated into this study, 79 dropped out during the first 5 years of treatment. The primary reasons for not continuing treatment were the lack of recurrence of initial clinical symptoms after several years of HRT or fear of potential side effects of HRT. These patients were not included in statistical analysis. In the 4 women who developed irregular bleeding while under treatment, a dilation and curettage was performed. The tissue morphology showed benign endometrial polyps in 3 cases and a fourth woman was diagnosed as having a submucosal leiomyoma. None of these four women showed either endometrial hyperplasia or carcinoma. An increased incidence of amenorrhea was seen with the treatment groups (E=estrogen, P=progestin): high E/high P < low E/high P < high E/low P < low E/low P (see also Figure 6).

An inverse relationship was seen for the incidence of withdrawal bleeding. Incidences of irregular bleeding were reported in the low estrogen/low progestin group. The combinations of percutaneous estradiol and PROMETRIUM® used in this study were sufficient to protect the endometrium from hyperplasia and adenocarcinoma. Administration of oral micronized progesterone (200 mg/day) was sufficient to significantly reduce mitotic activity in the endometrial glandular cells with a maximal reduction noted after a mean of 11 days of progesterone exposure. The progesterone antiproliferative effects (decrease in epithelial mitotic activity) may be separated from other secretory changes (stromal pseudostratification and glandular secretion).

Figure 6- Bleeding patterns during the last 12 months of the 5.7 years[a] study according to different estradiol/progesterone treatments.



a: 5.7 years was the mean duration of treatment at the time of endometrial biopsy or hysteroscopy.

A double-blind, randomized, parallel-group study compared the efficacy and safety of PROMETRIUM® 200 mg and 300 mg with placebo, in the initiation of withdrawal bleeding in patients with secondary amenorrhea. The duration of treatment was 10 days, and the efficacy on withdrawal bleeding was determined over a 16-day period (10 treatment days plus 1 week following the final dose). Efficacy analysis was based on sixty women receiving either PROMETRIUM® 200 mg (100 mg x 2 capsules + 1 placebo capsule) (19 women), 300 mg (100 mg x 3 capsules) (20 women) or placebo (3 capsules) (21 women), once daily at bedtime. Patients were assessed for withdrawal bleeding from the beginning of treatment up to and including one week following the final dose. Efficacy of the progesterone treatment was determined by comparing each of the PROMETRIUM® groups to the placebo group with respect to the initiation of withdrawal bleeding.

Table 8 summarizes withdrawal bleeding results following treatment in all 3 groups. Ninety percent (90%) (18/20) of the patients in the PROMETRIUM® 300 mg group experienced withdrawal bleeding as compared to 53% (10/19) in the PROMETRIUM® 200 mg group and

24% (5/21) in the placebo group. The proportion of patients experiencing withdrawal bleeding in the PROMETRIUM® 300 mg group was significantly greater than in the placebo group (one-tailed $p<0.001$); whereas the PROMETRIUM® 200 mg group was not significantly different from the placebo group (one-tailed $p>0.05$). There was a significant difference between the two treatment groups (two-tailed $p=0.0253$). Approximately twice as many patients in the PROMETRIUM® 300 mg group had withdrawal bleeding as compared to the 200 mg group (90% vs. 53%).

Table 8: Withdrawal Bleeding with PROMETRIUM® and Placebo.

	PROMETRIUM 200 mg N=19	PROMETRIUM 300 mg N=20	Placebo N=21
Patients having withdrawal bleeding	53%	90%	24%
Average number of days until withdrawal bleeding	8.7	10.7	10.4

A single-blind, randomized, controlled study compared oral and percutaneous routes of administration of estrogen, given either with or without PROMETRIUM®, as HRT for menopause. Criteria of effectiveness included transformation of the endometrium and endocrine profiles. Sixty-three healthy postmenopausal women entered the study. Percutaneous estradiol (2.5 mg) or oral conjugated estrogens (0.625 mg) was administered daily to hysterectomized (31 women) and non-hysterectomized (32 women) women from day 1 to day 25 of a 28-day cycle. Non-hysterectomized women also received 200 mg PROMETRIUM® on day 12 to day 25 of the 28-day cycle. In all cases, no treatment was administered during days 26 to 28. The duration of treatment was 6 months. Blood samples were obtained from each participant prior to treatment and throughout the replacement therapy. Serum LH, FSH and progesterone were determined. The 32 non-hysterectomized women had endometrial biopsies obtained by curettage before and after 24 weeks of replacement therapy. Morphological evaluation was assessed by light microscopy.

No patients dropped out during this study. Addition of PROMETRIUM® increased the inhibitory effect of the estrogen preparations on both LH and FSH. Serum progesterone levels fluctuated between 6 and 10 nmoL/L for the day 12 to day 25 period of each cycle, which is characteristic of levels seen during late luteal phases. Serum LH concentrations were lowered to 67, 79, 62 and 67% of their pretreatment concentrations following transdermal estradiol + PROMETRIUM®, transdermal estradiol alone, oral conjugated estrogens + PROMETRIUM® and oral conjugated estrogens alone, respectively, while FSH serum levels were respectively decreased to 60, 80, 46 and 57% of pretreatment values. Mitotic activity remained low in all cases after three or more days of PROMETRIUM® treatment, and no patients showed cystic or glandular hyperplasia. The anti-proliferative endometrial control seen in patients receiving 200 mg PROMETRIUM® in addition to either estrogen preparation appeared sufficient in all patients. Most of the patients (47%) remained amenorrheic and 34% had regular withdrawal bleeding. PROMETRIUM® administration did not influence the activity of 17β-hydroxysteroid dehydrogenase as the conversion of estrone to estradiol was similar in both groups of women receiving oral conjugated estrogens with or without PROMETRIUM®.

Lindenfeld et al. evaluated the bleeding patterns with common regimens of HRT using two different progestogens in the Postmenopausal Estrogen and Progestin Interventions Trial (PEPI). A total of 875 women in the PEPI trial took either placebo, conjugated equine estrogen 0.625 mg, conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg in a continuous fashion, or conjugated equine estrogen 0.625 mg daily plus either cyclical MPA 10 mg or cyclical PROMETRIUM® 200 mg/day for 12 days per month. For 596 patients with a uterus, bleeding days, amounts, and episodes were recoded for 3 years. Conjugated equine estrogens plus PROMETRIUM® cyclical was associated with fewer excess episodes of bleeding than conjugated equine estrogen plus MPA continuous in the first 6 months. Quantities of bleeding for conjugated equine estrogen plus PROMETRIUM® cyclical were less than for conjugated equine estrogen plus MPA cyclical through 30 months and for the number of bleeding days through study end. The authors concluded that the bleeding measures for conjugated equine estrogen plus PROMETRIUM® cyclical showed consistent advantages over those for conjugated equine estrogen plus cyclical MPA in terms of quantity, length, and episodes of bleeding.

Kim et al. study design was to explore the differential threshold of the biologic endpoints of antiproliferation and secretory conversion of the endometrium by different regimes of oral PROMETRIUM®. Patients were given 300 mg PROMETRIUM® daily (8:00 am) or twice (8:00 am and 4:00 pm) daily from study days 1 through 14 after estrogen priming for 30 days. The pharmacodynamic effect was examined by endometrial biopsies with regards to histology, glycogen content of glands, ribosomal RNA, and nuclear estrogen receptors in glands, surface epithelium, and stroma. Dose-dependent increases in glandular glycogen, decrease in ribosomal RNA, and decrease in nuclear estrogen receptors were demonstrated. The authors concluded that sustained low concentrations of PROMETRIUM® probably are sufficient to inhibit endometrial overgrowth and hyperplasia. Ultimately, oral PROMETRIUM® can induce antiproliferative changes in the human endometrium at doses lower than those required for transformation of the endometrium to a full secretory state.

DETAILED PHARMACOLOGY

See **ACTION AND CLINICAL PHARMACOLOGY (Part I)**.

TOXICOLOGY

ESTROGEL®

Administration of percutaneous 17ß-estradiol to female rats, at a dose of 0.5 g/animal/day for 13 weeks, resulted in the disappearance of a normal oestral cycle after 4 weeks and the appearance of a permanent oestrus after 12 weeks. A higher dose of 2.5 g/animal/day produced the disappearance of a normal oestral cycle after 2 weeks and the appearance of a permanent oestrus after 4 weeks. The estrogenic stimulation resulted in a 12% decrease in ovarian weight and a 60% increase in uterine weight. Histological examination of 19 organs revealed no modification, which would imply a toxic effect.

17ß-estradiol (0.06%) did not produce allergic dermatitis in the guinea pig model. When 0.5 g of 17ß-estradiol (0.06%) was applied to 1 square inch of either intact or abraded skin of rabbits, no significant skin irritation was observed.

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Percutaneous application of 17ß-estradiol (2.5 g/100 g and 7.5 g/100 g body weight) to rats produced therapeutic effects in uterus and vagina, showing signs of oestrus without hyperplastic side effects.

PROMETRIUM®

The toxicology of micronized progesterone has been studied in rats, rabbits and dogs. The biological effects of micronized progesterone have been demonstrated by increased uterine weight, endometrium development and deciduoma formation in rats and rabbits pretreated with estradiol.

Acute Toxicity
Acute oral toxicity of micronized progesterone has been evaluated in rats and the LD 50 was estimated to be 1,000-2,000 mg/kg in males and 320-400 mg/kg in females.

Subacute Toxicity
Subacute oral toxicity in rats has been studied with daily doses of 40, 100 and 250 mg/kg for 4 weeks as well as daily doses of 5, 15, 45 and 135 mg/kg for 12 weeks. In both subacute studies no mortalities occurred at any treatment level and no toxic or untoward effects were observed at 5, 15, 40 and 45 mg/kg. Signs of sedation, relaxation and coma were seen at higher dose levels (135 and 250 mg/kg) and salivation was seen with a dose of 100 mg/kg. Dose related weight gain was observed in females at the 100 and 250 mg/kg/day dosage. Hematological studies revealed modest decreases in circulating proteins after 3 months, with inconsistent effects on white blood cell counts. No other significant treatment related effects were observed in clinical signs or histopathology in either study.

In dogs, the subacute oral toxicity of micronized progesterone was studied at daily doses of 50, 125 and 325 mg/kg for 12 weeks. No mortalities were observed at any dose level. Treatment related effects included irritability and sedation in animals receiving 325 mg/kg and serum biochemical alterations at all levels of treatment. Changes in serum cholesterol, lipoproteins, total lipids and electrolyte balance were observed in the treated animals. Target tissue effects of micronized progesterone in treated animals included histopathological findings such as adenosic disease of the breast, ovarian cysts and cystic dysplasia of the endometrium. Treatment related histological changes were not observed in other tissues.

Carcinogenicity
Subcutaneous implantation of progesterone pellets in mice resulted in increases in ovarian granulosa cell tumors and endometrial sarcomas, metaplasia in the endocervical mucosa, squamous cell carcinomas of the cervicovaginal region and hyperplastic nodules of the mammary gland. The findings of tumors in the reproductive tissues of rodents are consistent with that observed with other progestational compounds.

Female beagle dogs, treated with progesterone administered by SC or IM injection for up to four years, developed endometrial and mammary hyperplasia (SC injection) and mammary gland nodules, including two carcinomas (IM injection). The Food and Drug Administration of the United States has concluded that the female Beagle is not an appropriate model for mammary carcinogenicity testing of progestins.

Mutagenicity
Progesterone was negative *in vitro* for point mutations in the Ames test, in *E. coli* bacteria, and in the mouse lymphoma forward mutation assay.

Progesterone did not cause mitotic disturbances or chromosome aberrations in Chinese hamster fibroblast cells in culture and did not cause an increase in unscheduled DNA synthesis in hepatocytes from male Fischer 344 rats in culture.

Progesterone was negative in assays for chromosome damage using human female leukocytes, or by the sister chromatid exchange (SCE) assay in human female peripheral blood lymphocytes (HPBL) or in human fibroblast cells.

Chromosome changes were observed in Chinese hamsters receiving SC injections of progesterone for up to four weeks, and in the testes of male mongrel dogs injected IM every other day for six weeks. Since the doses in these studies would have produced blood levels of progesterone in the endogenous range, the toxicological significance of the results is unclear.

Reproduction and Teratology
Administration of progesterone by SC injection to pregnant mice resulted in a decrease in sexual behavior in male offspring with no changes to internal or external genitalia, and an increase in aggressive behavior in female offspring. No abnormalities of internal or external genitalia were observed in the offspring of rats treated with progesterone by SC injection.

No adverse effect on egg development was observed following oral (gavage) administration of progesterone to rabbits three days before or after mating. SC dosing of pregnant rabbits also had no adverse effect on egg development, while SC dosing two days prior to mating induced complete degeneration of eggs. Single SC injection to rabbits before mating did not impair fertility but led to embryonic death by day 4 of gestation.

Administration of progesterone by IM injection to pregnant rhesus monkeys did not cause any adverse effects on pregnancy or on the incidence of anomalies in the offspring.

<u>Human Data</u>
No increased risk of malformations has been reported in several epidemiological, retrospective and prospective studies of women treated with progesterone prior to and during the first trimester of pregnancy.

However, during post marketing use, one case of cleft palate was reported following first trimester use (causality not established). Rare cases of fetal death (causality not established) have also been reported.

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PART III: CONSUMER INFORMATION

ESTROGEL PROPAK™
17ß-estradiol, as estradiol hemihydrate, transdermal gel
and
Progesterone capsules

This leaflet is part III of a three-part "Product Monograph" published when ESTROGEL PROPAK™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ESTROGEL PROPAK™.

Please read this leaflet carefully before you start taking ESTROGEL PROPAK™ and each time you have your prescription refilled. It contains information regarding possible risks of hormone replacement therapy obtained from the results of the Women's Health Initiative Study.

This information leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment. If you have any questions or concerns, consult your doctor or your pharmacist.

ABOUT THIS MEDICATION

What the medication is used for:

There are two products in this package: ESTROGEL® (17ß-estradiol, as estradiol hemihydrate, transdermal gel) and PROMETRIUM® (progesterone capsules) and they have different uses.

ESTROGEL PROPAK™ (17ß-estradiol and micronized progesterone) is indicated in patients for whom treatment with both ESTROGEL® and PROMETRIUM® is appropriate.

ESTROGEL®

ESTROGEL® is approved for use in the following situation:

- replacement of estrogen in menopausal women with symptoms of menopause, which may include hot flushes, disturbed sleep and vaginal dryness.

ESTROGEL® should not be used by women who have not had a hysterectomy (surgical removal of the uterus) unless prescribed in association with a progestin medication.

PROMETRIUM®

PROMETRIUM® (micronized progesterone) is approved for use in the following situation:

- In women with an intact uterus (have not had surgery to remove the uterus) who are using estrogen replacement therapy for menopause

Progesterone, as in PROMETRIUM® capsules, has a strong influence on the inner lining of the uterus and is used with estrogen therapy during and after menopause. The purpose of using progesterone is to protect the inner lining of the uterus from overgrowth caused by estrogen therapy.

ESTROGEL PROPAK® 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:

ABOUT MENOPAUSE
Menopause is not a disease. Menopause is a natural, pre-determined point in a women's life when the ovaries decrease their production of the female hormones, estrogen and progesterone. In most women, this occurs between the ages of 45 and 55 or sooner if the ovaries have been removed by surgery.

The symptoms associated with menopause vary for every woman. The most common symptom is hot flushes/flashes. Other symptoms some women may develop after menopause include insomnia (reduced quality of sleep) and vaginal atrophy (dryness). Your doctor can provide you with further information on menopause.

ESTROGEL PROPAK™ contains 2 medicines used together.

The active ingredient in ESTROGEL® is estradiol, a natural female hormone. In healthy women of childbearing age, estradiol is the main estrogen produced by the ovaries. When using ESTROGEL®, two pump pressures will deliver 2.5 gram of gel, which provides 1.5 milligram of the estrogen substance estradiol. The gel should be applied to the skin over a large area (>2000 cm2), such as both arms. It will be quickly absorbed into the underlying layers of the skin. Over time, the estradiol will be slowly released into the bloodstream.

ESTROGEL® does not contain progestins.

The active ingredient in PROMETRIUM® capsules is progesterone, a natural female hormone. In healthy women of childbearing age, progesterone is produced by the ovaries each month during the second part of the menstrual cycle. Progesterone plays a role in the monthly shedding of the inner lining of the uterus (endometrium) and the menstrual bleeding that follows.

For information on the dose and how frequently these products should be taken, please see PROPER USE OF THIS MEDICATION below.

When it should not be used:
Do not use ESTROGEL PROPAK™ if you:

- have an allergic or an unusual reaction to progesterone, soya, peanut or to any of the ingredients in PROMETRIUM®;
- have had an allergic or unusual reaction to ESTROGEL® or to any of its ingredients;
- have liver disease;
- have or have had cancer or abnormalities of the breast or uterus (endometrial cancer);
- have overgrowth of the lining of the uterus (endometrial hyperplasia);
- have experienced undiagnosed or unexpected vaginal bleeding;
- are pregnant or suspect you may be pregnant;
- are breast-feeding;
- have a history of coronary heart disease (including heart attack) or stroke;
- have migraine headaches;
- have a history of blood clots or have had abnormal increase in blood clotting;
- have active thrombophlebitis (inflammation of the veins);
- have partially or completely lost vision due to blood vessel disease of the eye
- known or suspected hormone dependant cancer.

What the medicinal ingredient is:

ESTROGEL PROPAK™ contains two medicines. One is ESTROGEL® which contains 17β-estradiol. The other is PROMETRIUM® which contains micronized progesterone

What the nonmedicinal ingredients are:

ESTROGEL® also contains carbopol 980, ethanol, purified water and triethanolamine.

PROMETRIUM® also contains sunflower oil, gelatin, glycerin, soya lecithin (may contain traces of medium chain triglycerides), titanium dioxide.

What dosage forms it comes in:

ESTROGEL® is packaged in 80 g metered-dose pumps. Each metered-actuation delivers 1.25 g of gel (0.75 mg of 17ß-estradiol).

Each PROMETRIUM® capsule contains 100 mg (milligrams) of micronized progesterone.

ESTROGEL PROPAK™ (17ß-estradiol and micronized progesterone) is available in a carton containing one ESTROGEL® 80 g metered-dose pump and one blister pack of 30 PROMETRIUM® 100 mg capsules.

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 ingredient) 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* .

The Women's Health Initiative Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of probable dementia (madness) in postmenopausal women 65 years of age or older.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke or dementia.
- Estrogens with or without progestins should be used at **the lowest effective dose** and for **the shortest period of time** possible. Regular medical follow-up is advised**.**

Breast Cancer
The results of the WHI trial indicated an increased risk of breast cancer in 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 postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer. In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting hormone replacement therapy.

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

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

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

The purpose of adding a progestin medication to estrogen therapy is to reduce the risk of endometrial hyperplasia.

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

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

Ovarian Cancer
In some studies the use of *estrogen-alone* therapy 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 estrogen therapy by post menopausal women has been associated with an increased-risk of gallbladder disease requiring surgery.

Dementia
The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo. The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral e*strogen-alone* compared to women taking placebo.

Contact Sensitization
Products applied onto the skin may result in sensitization. Although it is extremely rare, skin sensitization may evolve into severe hypersensitivity reaction with continued use of the gel.

BEFORE you use ESTROGEL PROPAK™ talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to PROMETRIUM® or any of its ingredients (see What the medicinal ingredient is/ What the nonmedicinal ingredients are), or are allergic to soya or peanut or to any other substances or medications;
- have a history of allergy or intolerance to ESTROGEL® or any of its ingredients, or to any medications or other substances;
- 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 personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer);
- have a history of endometrial hyperplasia (overgrowth of the lining of the uterus);
- have experienced undiagnosed or unusual vaginal bleeding;
- have experienced pressure or pain in your abdomen or pelvis;
- have a history of uterine fibroids (abnormally thick tissue in the uterus) or endometriosis (disorder of the uterine lining);
- have a personal or family history of blood clots, or a personal history of heart disease, heart attack or stroke;
- have a history of migraine headache;
- have a personal history of active thrombophlebitis (inflammation of the veins);
- have or have had a partial or complete loss of vision due to blood vessel disease of the eye;
- are pregnant or may be pregnant;
- smoke;
- have a history of high blood pressure;
- have a history of kidney disease, epilepsy (seizures) or asthma;
- 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 (a type of fat in the blood);
- have a history of depression.
- have had a hysterectomy (surgical removal of the uterus)
- 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.
- breastfeeding

PROMETRIUM® may cause some people to feel dizzy or sleepy, 1-4 hours after ingestion of the capsules. Therefore, before you drive or do anything else that requires alertness, make sure you are not experiencing these side effects.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ESTROGEL® include: Barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone or rifampin, atorvastatin, antibiotics, aminoglutethimide, some herbal products (e.g. St. John's wort), phenobarbital, phenytoin troglitazone, ascorbic acid, acetaminophen, oral contraceptives containing ethinyl estradiol, progestin.

Estrogens may diminish the effectiveness of anticoagulant (substance that prevents coagulation), antidiabetic (drugs treating diabetes mellitus) and antihypertensive agents (drugs treating high blood pressure).

Some medications (such as certain anti-seizure medications or antibiotics) may affect how PROMETRIUM® Capsules work. PROMETRIUM® Capsules may also affect how your 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.

HOW AND WHEN TO APPLY ESTROGEL®

PROPER USE OF THIS MEDICATION

Usual dose:

ESTROGEL®

Do not apply ESTROGEL® on the breasts since this may cause unwanted effects and discomfort. Do not apply ESTROGEL® to the face or to irritated or damaged skin.

The recommended dosage of ESTROGEL® is two pump pressures (2.5 g) per day on a cyclic schedule from day 1 to day 25 of each calendar month or from day 1 to day 21 of a 28-day cycle. ESTROGEL® may be applied either in the morning or evening after washing, but preferably about the same time each day. If your periods have stopped, or are irregular, you can start using ESTROGEL® at any time.

Under the supervision of your doctor, the dose of ESTROGEL® can be adjusted to meet your individual needs. Attempts to adjust the necessary dosage should be made after two months of treatment. Breast tenderness and/or unexpected bleeding are generally signs that the dose is too high and needs to be lowered. However, if the selected dose fails to control your menopausal symptoms, a higher dose may be prescribed.

You and your doctor should talk regularly about whether you still need treatment with estrogen.

ESTROGEL® Pump:

- Remove the large pump cover. When you open a new pump, press on the pump once or twice in order to prime the pump and discard these doses.

- Press firmly on the pump once, collect the gel in your hand and apply the gel on one arm, as illustrated. Repeat and apply the gel on the opposite arm.

- ESTROGEL® should be applied using clean hands onto clean, dry skin. The gel should be spread over a large area of skin (at least 2,000 cm^2), which corresponds to approximately 4 times the size of your hand. It is recommended to apply ESTROGEL® to both arms, as illustrated. Other recommended areas of application are the abdomen or the inner thighs, as illustrated. It is not necessary to rotate the site of administration. **Do not apply ESTROGEL® on the breasts since this may cause unwanted effects and discomfort.** Do not apply ESTROGEL® to the face or to irritated or damaged skin.

- Allow the gel to dry for 2 minutes before covering with clothes. ESTROGEL® does not stain and does not smell.

- The pump contains enough gel for approximately 1 month's use (i.e. 64 metered-doses) at the recommended dose of two pumps/per day (2.5 g). After that, the amount of gel delivered may be lower and thus, it is recommended to change the pump.

- Always replace the small protective cap back in the tip of the pump as well as the large pump cover after each use, as illustrated.

PROMETRIUM®

Take PROMETRIUM® (micronized progesterone) only as directed by your doctor or pharmacist.

Hormone Replacement Therapy for Menopause

The recommended dose is 2 capsules (200 mg) of PROMETRIUM® per day for the last 14 days of estrogen treatment each cycle or 3 capsules per day (300 mg) for the last 12-14 days of estrogen treatment each cycle. If you are being treated with 2 capsules (200 mg) a day you should take them both at bedtime. If you are being treated with 3 capsules (300 mg) a day, you should split the daily dose in two parts by taking one capsule in the morning and two at bedtime. PROMETRIUM® should be started on the first estrogen cycle. The length of time that you will take PROMETRIUM® will depend of the length of time that you are treated with estrogen. PROMETRIUM® should be taken as long as you take estrogen and you have an intact uterus (have not had surgery to remove the uterus).

A few days after completing a PROMETRIUM® course of 3 capsules daily, the inner lining of the uterus will usually shed. This is accompanied by-vaginal bleeding (resembling a normal monthly period). With a dosage of 2 capsules daily, many women will not have such vaginal bleedings, although the lining of the uterus will also be protected against overgrowth.

Overdose:

In case of drug overdose, contact your doctor, or a poison control centre, or go to the emergency room of the hospital near you immediately, even if there are no symptoms.

When someone accidentally takes too much ESTROGEL®, the following symptoms may arise: nausea (urge to vomit), breast discomfort, fluid retention, abdominal cramps, headache, dizziness, bloating or vaginal bleeding in women.

When someone accidentally takes too much PROMETRIUM® (micronized progesterone), the following symptoms may arise: nausea, vomiting, sleepiness, dizziness, depressive mood, tiredness, acne and hairiness.

Missed Dose:

ESTROGEL®
If a dose of this medication has been missed, it should be taken as soon as possible. However if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double dose. If you are in doubt, contact your healthcare provider.

PROMETRIUM®
If you are being treated with 2 capsules a day (total dose at bedtime) and you forget to take this dose, you should take one capsule the following morning and continue taking the rest of the capsules as prescribed. If you are being treated with 3 capsules a day and you forget to take a morning or evening dose, you should not take the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very rarely, skin irritation can occur with ESTROGEL®.

Depending on the dosage of estrogen and the sensitivity of the patient, the following side effects are possible:

- genital bleeding or spotting (minor vaginal bleeding) in between the normal periods,
- headaches or depressive mood;
- breast tenderness/swelling;
- nausea (urge to vomit), abdominal discomfort (cramps, pressure, pain);
- worsening of varicose veins (visible and bulging veins);
- fatigue (tiredness).

Other side effects that have been observed with estrogen and progestin combinations in general are:

- water retention (bloating, swelling);
- (endometrial hyperplasia) overgrowth of the lining of the uterus;
- gallbladder disorder, impaired liver function, jaundice (yellowing of the eyes or skin);
- menstrual cramps;
- vaginal itching/discharge;
- pain during sexual intercourse;
- pain on urination or difficulty urinating;
- premenstrual syndrome (PMS);
- inflammation of the bladder;
- brown, blotchy spots on exposed skin (pregnancy mask);
- skin rash, tender red lumps or nodules or other skin reactions;
- loss of hair, hairiness;
- acne;
- palpitations (unpleasant sensation of irregular and/or forceful beating of the heart);
- pain, swelling or redness of the calf or leg which may indicate a blood clot;
- chest pain or shortness of breath which may indicate a blood clot;
- increase in blood pressure;
- depression;
- nervousness;
- irritability;

- visual disturbances, intolerance to contact lenses;
- changes in appetite and body weight;
- change in sexual drive;
- pain in the joints and muscles, usually lasting only 3-6 weeks.

Depending on the dosage of PROMETRIUM® (micronized progesterone) and the sensitivity of the patient, the following side effects are possible: genital bleeding or spotting (minor vaginal bleeding) in between the normal periods (mainly during the first two months); irregular menstrual periods; dizziness or vertigo; sleepiness; abdominal discomfort (cramps, pressure, pain); nausea (urge to vomit); fatigue (tiredness); aggravation of migraine headaches, headaches or depressive mood; lightheadedness (feeling faint); breast tenderness/swelling; liver disease.

Side effects observed in women taking progestins in general: a severe allergic reaction which may include hives, itchiness, skin redness, swelling, wheezing, increase heart rate and difficulty breathing; rash with or without itching; rare cases of loss of consciousness; hot flashes; impaired concentration; confusion; swelling; and difficulty with speech.

During your first 2-4 months of HRT, you may experience minor unscheduled vaginal bleeding (at times other than when you would expect a normal period). This is a normal response of your body as it adjusts to the return of estrogen and progesterone to the levels that were seen before menopause. Should unscheduled vaginal bleeding persist, you should consult your doctor.

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

Frequency	Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
At any frequency	Abnormal increase in blood clotting;			√
	Increase in blood pressure;		√	
	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			√
	Migraine			√
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg (any of these, alone or in combination)			√
	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 ESTROGEL PROPAK™, contact your doctor or pharmacist.

HOW TO STORE IT

ESTROGEL PROPAK™ should be stored at room temperature between 15°C and 30°C.

ESTROGEL® should be stored with the cap on securely.

The date the capsules should be used by is printed on the strip after the term "Exp." (expiry date).

Keep out of reach of children.

GENERAL THINGS TO REMEMBER

1. This medication has been prescribed only for your current medical problem. Do not use it for other medical problems.
2. Do not allow other people to use your medications and do not use medications meant for other people.
3. Tell any doctor treating you what medications you are taking. Always carry a medical information card stating which medications you are using. This can be very important in case you are involved in an accident.
4. Return unused medications to the pharmacy for safe disposal.
5. Make sure that other people you live with or who look after you read this information.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - **Mail to:** Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

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

MORE INFORMATION

Also, you can report any suspected adverse reactions associated with the use of health products to Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at 1-800-567-2594
- Fax toll-free to 1-800-369-3090, or

  Mail to: Merck Canada Inc.
  Pharmacovigilance
  P.O. Box 1005
  Pointe-Claire–Dorval, QC H9R 4P8

This document plus the full product monograph, prepared for health professionals, can be found at:
http://www.merck.ca
or by contacting the sponsor, Merck Canada Inc.,
at: 1-800-567-2594.

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