PRODUCT MONOGRAPH

[Pr]pms-ESTRADIOL VALERATE INJECTION

Estradiol Valerate

10 mg/mL

Estrogen

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PRODUCT MONOGRAPH

[Pr]pms- ESTRADIOL VALERATE INJECTION

(Estradiol Valerate)
10 mg/mL

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular	Injection / 10 mg/mL	Sesame Oil *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

pms-ESTRADIOL VALERATE INJECTION is indicated in the treatment of:

I. amenorrhea (primary and secondary);
II. deficiency syndromes (castration, primary ovarian failure, menopause);
III. local manifestations of estrogen deficiency (senile vaginitis, pruritus vulvae);
IV. (for palliation only) of inoperable progressing prostatic carcinoma in males.

When prescribing solely for the treatment of symptoms of senile vaginitis and pruritus vulvae, topical vaginal products should be considered.

pms-ESTRADIOL VALERATE INJECTION should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

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

Pediatrics (< 16 years of age): Estrogens should be used with caution in young patients in whom bone growth is not complete since estrogens can affect the bone growth plates. pms-ESTRADIOL VALERATE INJECTION is not indicated for use in children.

CONTRAINDICATIONS

Estrogens should not be administered to patients with:

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

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.[1-3]

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.[1]

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo. [2]

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

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for the **shortest period possible** for the approved indication.

General

In the absence of comparable data, the risks of HRT should be assumed to be similar for all estrogens and estrogen/progestin combinations.

Carcinogenesis and Mutagenesis

Breast cancer

Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period there were:

· 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).[1]

The WHI study 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.[3]

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

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease (see **Contraindications**). There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/ or atypical hyperplasia at breast biopsy). Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

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

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

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

Endometrial hyperplasia & endometrial carcinoma

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

Ovarian cancer

Some recent epidemiologic studies have found that the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or

more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular

The results of the Heart and Estrogen/Progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[1,4,5] The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.[1,2]

WHI trial findings

In the combined *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).[1]

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

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

HERS and HERS II findings

In the Heart and Estrogen/progestin Replacement 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.[4]

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.[5]

Blood pressure

Women using hormone replacement therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure

in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Ear/Nose/Throat
Otosclerosis

Estrogens should be used with caution in patients with otosclerosis.

Endocrine and Metabolism

Glucose and lipid metabolism

A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients, or those with a predisposition to diabetes, should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

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

Heme metabolism

Women with porphyria need special surveillance.

Calcium and phosphorus metabolism

Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

In male patients, hypercalcemia may develop.

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

Endometriosis

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

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.

Vaginal bleeding

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

Hematologic

Venous thromboembolism

Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.[1]

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.[2]

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition) and severe obesity (body mass index > 30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

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

If feasible, estrogens 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 estrogens may cause an exacerbation of this condition.

Jaundice

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

Liver function tests

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under **Monitoring and Laboratory Tests**.

Immune

Angioedema

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

Systemic lupus erythematosus

Particular caution is indicated in women with systemic lupus erythematosus.

Neurologic

Cerebrovascular insufficiency

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

Dementia

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

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral estrogen-alone) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline. [6,7]

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) [6]

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. [7]

When data from the *estrogen plus progestin* arm of the WHIMS and the e*strogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo). [7]

Epilepsy

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

Ophthalmologic

Visual abnormalities

If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Psychiatric

Discontinue the medication in patients with a history of psychiatric abnormalities if exaggeration of symptoms occurs.

Renal

Fluid retention

Estrogens may cause fluid retention.

Therefore, particular caution is indicated in cardiac, 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.

Sexual Function/Reproduction

Prolonged high doses of estrogens will inhibit anterior pituitary function. This should be borne in mind when treating patients in whom fertility is desired.

In male patients, gynecomastia (breast enlargement) or soreness of the breast, reduced potency and feminization may occur.

Special Populations

Pregnant Women: Estrogens/progestins should not be used during pregnancy (see **CONTRAINDICATIONS**).

Nursing Women: Estrogen may be excreted in the mother's milk and an estrogenic effect upon the nursing infant has been described Estrogen should not be used during lactation (See **CONTRAINDICATIONS**).

Pediatrics: Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete. pms-ESTRADIOL VALERATE INJECTION is not indicated for use in children.

Geriatrics (> 65 years of age): Of the total number of subjects in the conjugated equine estrogens in combination with medroxyprogesterone acetate substudy of the Women's Health Initiative study (WHI), 44% (n=7320) were 65 years and over, while 6.6% (n=1,095) were 75 and over. No significant differences in relative risks were observed between subjects 65 years and over compared to younger subjects. There was a higher relative risk of stroke and invasive breast cancer in women 75 and over compared to younger subjects.

Monitoring and Laboratory Tests

Before pms-Estradiol Valerate Injection is administered, the patient should have a complete physical examination including blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests. Before starting treatment pregnancy should be excluded. The first follow-up examination should be done within three to six months of initiation of treatment

to assess response to treatment. Thereafter, examinations should be made at intervals of at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See **Warnings and Precautions** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

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

Blood and lymphatic system disorders

Altered coagulation tests (see **Warnings and Precautions, Drug-Laboratory Tests Interactions**).

Cardiac disorders

Palpitations; increase in blood pressure (see **Warnings and Precautions**); coronary thrombosis.

Endocrine disorders

Increased blood sugar levels; decreased glucose tolerance.

Eye disorders

Neuro-ocular lesions (e.g retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.

Gastrointestinal disorders

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).

General disorders and administration site conditions

Fatigue; changes in appetite; changes in body weight; change in libido.

Hepatobiliary disorders

Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

Musculoskeletal and connective tissue disorders

Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous system disorders

Aggravation of migraine episodes; headaches; dizziness; neuritis.

Psychiatric disorders

Mental depression; nervousness; irritability.

Renal and urinary disorders

Cystitis; dysuria; sodium retention; edema.

Reproductive system and breast disorders

Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea ; vaginal itching/discharge; dyspareunia ; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

Skin and subcutaneous tissue disorders

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

Vascular disorders

Isolated cases of: thrombophlebitis; thromboembolic disorders.

Clinical Trial Adverse Drug Reactions

Data are not available.

Less Common Clinical Trial Adverse Drug Reactions

Data are not available.

Abnormal Hematologic and Clinical Chemistry Findings

Data are not available.

Post-Market Adverse Drug Reactions

Post-marketing and/or case reports for Estradiol include: liver function tests and leg pain.

DRUG INTERACTIONS

Overview

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

Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

Drug-Drug Interactions

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

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

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

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

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

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

Drug-Herb Interactions

It was found that some herbal products (e.g St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be made aware of other non-prescription products concomitantly used by the patient, including herbal and natural products, obtained from the widely spread Health Stores.

Drug-Food Interactions

CYP3A4 inhibitors such as grapefruit juice may increase plasma concentrations of estradiol and may result in side effects.

Drug-Laboratory Test Interactions

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

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine_induced platelet aggregability; decreased antithrombin III.
- increased thyroxine_binding globulin (TBG), leading to increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay; T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered;
- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged.
- impaired glucose tolerance
- increased serum triglycerides and phospholipids concentration;

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

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

The lowest effective dosage should be used for the shortest period possible for the recognized indication. The requirement for estrogen therapy should be reassessed periodically.

Excluding the indication for use of pms-ESTRADIOL VALERATE INJECTION (estradiol valerate) in males with inoperable progressing prostatic carcinoma, malignancies that are hormone-sensitive should be ruled out before hormone therapy is started.

Recommended Dose and Dosage Adjustment

For Women:

CYCLIC THERAPY SCHEDULE (28-day cycle; repeated every 4 weeks)

Day 1 of each cycle: 20 mg pms-ESTRADIOL VALERATE INJECTION
2 weeks after Day 1: 5 mg pms-ESTRADIOL VALERATE INJECTION
4 weeks after Day 1: This is Day 1 of next cycle.

Monitoring

Due to its intramuscular route of administration, estradiol blood levels following administration of pms-ESTRADIOL VALERATE INJECTION may vary among patients. Therefore, it may be appropriate to measure estradiol blood levels in order to reduce the risk of endometrial complications. Estradiol blood levels should remain in the range seen in the early follicular phase of the menstrual cycle. Frequency of monitoring of estradiol blood levels should be determined by the treating physician.

Efficacy of progestin therapy in women with intact uteri should be periodically monitored by ultrasound determination of endometrial thickness. Frequency of endometrial monitoring should be determined by the treating physician.

Amenorrhea (primary and secondary):

See CYCLIC THERAPY SCHEDULE.
Start therapy after excluding diagnosis of early pregnancy or endometrial pathology on the basis of presenting symptomatology.
Repeat every 4 weeks. Stop after 4 cycles.

To determine onset of normal cyclic function, patient should be observed for 2 to 3 cycles after cessation of therapy.

Deficiency Syndroms (castration, primary ovarian failure, menopause):

See CYCLIC THERAPY SCHEDULE.

Start therapy any time. Repeat every 4 weeks. Stop after 4 cycles.

Local Manifestations of Estrogen Deficiency (senile vaginitis, pruritus vulvae):

See CYCLIC THERAPY SCHEDULE:

Start therapy any time. Repeat every 4 weeks. Stop after 4 cycles.

For Men:

(For palliation only) inoperable progressing prostatic carcinoma:

30 mg or more every 1 to 2 weeks.

Schedule and duration of treatment should be determined by the treating physician.

Close medical supervision is mandatory.

Soreness of the breast or gynecomastia may occur. Hypercalcemia may develop.

Missed Dose

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

Administration

In women with intact uteri, a progestin should be coadministered for a minimum of 12 to 14 days per cycle to avoid overstimulation of the endometrium and to prevent the development of endometrial hyperplasia. A progestin is not required for this purpose in hysterectomized women.

Care should be taken to inject pms-ESTRADIOL VALERATE INJECTION deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. By virtue of the low viscosity of the vehicle, pms-ESTRADIOL VALERATE INJECTION may be administered with a small gauge needle. A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however this does not affect the potency of the material.

OVERDOSAGE

Symptoms:
Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects.
Accidental overdosage may result in nausea, vomiting and abdominal cramps, headache, dizziness, breast discomfort,and general malaise. The transient hyperestrogenic effects may include severe temporary sodium and water retention, bloating or vaginal bleeding in women.

Treatment: Give symptomatic treatment.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.
Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacodynamics

Estrogens used in therapy are soluble in water and are well absorbed through the skin, mucous membranes, and gastrointestinal tract after release from the drug formulation.

Effects on vasomotor symptoms associated with estrogen deficiency
Hot flushes, feelings of intense heat over the upper trunk and face, with flushing of the skin and sweating occur in approximately 80% of women as a result of the decrease in ovarian hormones. These vasomotor symptoms are seen in women whether menopause is surgically induced or spontaneous. However, hot flushes may be more severe in women who undergo surgical menopause. Hot flushes can begin before the cessation of menses.

Effects on the Endometrium
The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. [11,12]

Effect on bleeding patterns
With a continuous therapy, several bleeding patterns may occur. These may range from absence of bleeding to irregular bleeding. If bleeding occurs, it is frequently light spotting or moderate bleeding.

Pharmacokinetics

Absorption
Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

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

When given orally, naturally occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first_pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

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

Special Populations and Conditions

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

Estrogen Pharmacology

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. Indirectly, they also contribute to the shaping of the skeleton, maintenance of tone and elasticity through the increase of collagen production in the supportive tissues of the heart, skin and urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Decline of ovarian estrogenic and progestogenic activity at the end of the menstrual cycle can result in menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or anovulatory cycle, estrogen is the primary determinant in the onset of menstruation.

Estrogen drug products act by regulating the transcription of a limited number of genes. They may act directly at the cell's surface via non "estrogen receptor" mechanism or directly with the estrogen receptor inside the cell. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the

observed effects. Estrogen receptors have been identified in the wall of blood vessels, in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

It is necessary to protect against endometrial hyperplasia during long term therapy with estrogens in women with intact uteri. The results of clinical studies indicate that the addition of a progestin to an estrogen replacement regimen for more than 10 days per cycle reduces the incidence of endometrial hyperplasia and the attendant risk of adenocarcinoma in women with intact uteri. The addition of a progestin into an estrogen replacement regimen has not been shown to interfere with the efficacy of estrogen replacement therapy for its approved indications.

STORAGE AND STABILITY

Store the vials between 15°C and 30°C. Low temperatures may result in separation of some crystalline material, which dissolves readily on rewarming. pms-ESTRADIOL VALERATE INJECTION should not be used after the expiry date shown on the package label.

Keep this medicine out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-ESTRADIOL VALERATE INJECTION contains the following medicinal ingredient: estradiol valerate.
pms-ESTRADIOL VALERATE INJECTION contains the following non-medicinal ingredients: chlorobutanol 0.5% w/v and sesame oil.

Supplied

pms-ESTRADIOL VALERATE INJECTION is supplied in vials of 10 mL.
Each mL of sterile suspension contains: estradiol valerate 10 mg in sesame oil plus 0.5% chlorobutanol as a preservative.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

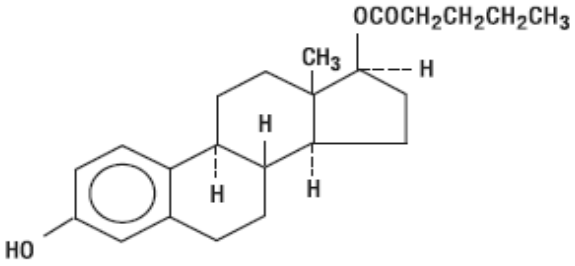
Proper name: Estradiol Valerate

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

Molecular formula: $C_{23}H_{32}O_3$

Molecular mass: 356.50

Structural formula:



Description: Estradiol Valerate Injection, USP contains estradiol valerate, a long-acting estrogen in sterile oil solutions for intramuscular use. These solutions are clear, colourless to pale yellow.

CLINICAL TRIALS

Pivotal Clinical Trials

There are no available pivotal clinical trial data for pms-ESTRADIOL VALERATE INJECTION.

DETAILED PHARMACOLOGY

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

TOXICOLOGY

Preclinical safety data

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

Most of the documented effects of exogenously administered estradiol in animal studies have been consequences of the administration of supraphysiological doses and are consistent with an exaggerated pharmacological response (most notably the promotion of tumours in oestrogen-responsive tissues). However, long-term unopposed treatment with physiological doses of estradiol may lead to hyperplastic changes in oestrogen-dependent reproductive organs like the uterus.

REFERENCES

SELECTED BIBLIOGRAPHY

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA. 2002; 288(3):321-333.

2. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative randomized controlled trial. JAMA. 2004; 291(14):1701-1712.

3. Chelbowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. The Women's Health Initiative Randomized Trial. Influence of Estrogen plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. JAMA. 2003; 289(24):3243-3253.

4. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998; 280(7):605-613.

5. Grady S, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/progestin replacement study follow-up (HERS II). JAMA. 2002; 288(1):49-57.

6. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA. 2003; 289(20):2651-2662.

7. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. Women's Health Initiative Memory Study. JAMA. 2004; 291(24):2947-2958.

8. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford S.A.A., Black H, et al. Effects of conjugated equine estrogens in postmenopausal women with hysterectomy - The Women's Health Initiative Randomized Controlled Trial. JAMA 2004 April 14;291(24):1701-12.

9. Beral V. Million W, Bull D, Green J, Reeves G (2007). Ovarian cancer end hormone replacement therapy in the Million Women Study. Lancet 69(9574); 1703-10.

10. Lacey JV, Brinton LA, Leitzmann MF, Mouw T, Hollenbeck A, Schatzkin, A, et al. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health- AARP Diet and Health Study Cohort, J Natl Cancer Inst. 2006;98:1397-1405.

11. Morrow CP, Townsend DE. Cancer of the uterine corpus. In: Synopsis of gynecologic oncology. New York: John Wiley and Sons, 2nd ed.; 1981. p. 133-185.

12. Kurman RJ, Kaminsk PF, Norris HJ. The behavior of endometrial hyperplasia: A long-term study of "untreated" hyperplasia in 170 patients. Cancer. 1985;56:403-12.

13. José Remohi, M.D.; Adela Vidal, M.D.; Antonio Pellicer, M.D. Oocyte donation in low responders to conventional ovarian stimulation for in vitro fertilization. Instituto Valencianco de Infertilidad, and Department of Pediatrics, Obstetrics, and Gynecology, Valencia University School of Medicine, Valencia, Spain
Fertil Steril 1993;59:1208-15

14. Prescribing Information Delestrogen® (Estradiol Valerate Injection, USP), December 2, 2003.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

pms-Estradiol Valerate Injection
(Estradiol Valerate)
10 mg/mL

IMPORTANT PLEASE READ

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

ABOUT THIS MEDICATION

What the medication is used for:

- To treat amenorrhea (absence of periods – either periods never start or cease to occur).
- To treat estrogen deficiency syndromes (including menopause, following surgical removal of the ovaries and other conditions in which a woman's ovaries do not produce enough estrogen naturally).
- To treat conditions of the vagina and external genitalia associated with low estrogen levels.

  If you use pms-Estradiol Valerate Injection only to treat symptoms of the vagina and external genitalia associated with low estrogen levels, talk with your healthcare provider about whether a vaginal (topical) treatment might be better for you.
- To treat inoperable progressing prostatic cancer in men.

pms-ESTRADIOL VALERATE INJECTION should not be used by women with intact uteri unless it is prescribed in association with a progestin.

pms-ESTRADIOL VALERATE INJECTION 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 after starting treatment. Your visit may include a blood pressure check, a breast exam and 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.

Close medical supervision is mandatory for men when pms-ESTRADIOL VALERATE INJECTION is used for the treatment of prostate cancer.

You should carefully discuss all of the risks and benefits of estrogen therapy with your physician. You and your physician should talk regularly about whether you still need treatment with estrogen. The dosage, frequency (how often) and duration of your treatment with pms-ESTRADIOL VALERATE INJECTION should be based on the reason for use, as carefully determined by your physician.

What it does:

Estradiol valerate is a form of estrogen. Estrogen is a female sex hormone produced by the ovaries. During and after menopause, and in certain other medical conditions, the amount of estrogen produced by the body is reduced. pms-ESTRADIOL VALERATE INJECTION is intended for use as estrogen-replacement therapy for women with symptoms related to menopause or for women with other conditions in which too little estrogen is produced naturally. It is also intended for use in men in the treatment of inoperable progressing cancer of the prostate.

When it should not be used:

pms-ESTRADIOL VALERATE INJECTION **should not** be used if you:

- If you have had an unusual allergic response to estrogen or to any of the ingredients in the tablet. For a complete listing see **What the medicinal ingredient is and What the non-medicinal ingredients are** section of the product monograph;
- In the presence of liver disease;
- If you have had or have cancer of the breast or uterus;

- If you have been diagnosed with overgrowth of the lining of the uterus;
- If you have abnormal vaginal bleeding;
- If you are pregnant or think you may be pregnant;
- If you have had or have a problem with abnormal blood clots forming in your blood vessels. This may cause painful inflammation of the veins (thrombophlebitis) or blockage of a blood vessel in the legs (deep vein thrombosis), lungs (pulmonary embolism) or other organs;
- Have had partial or complete loss of vision due to blood vessel disease of the eye;
- If you experience migraine headaches;
- If you have had or have heart disease, a stroke or heart attack;
- If you are breastfeeding.

What the medicinal ingredient is:

Estradiol Valerate

What the non-medicinal ingredients are:
Chlorobutanol (preservative) and Sesame Oil

What dosage forms it comes in:

Vials of 10 mL
Each mL contains 10 mg Estradiol Valerate
For injection

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) is a large clinical study that assessed the benefits and risks of oral combined estrogen plus progestin therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

Therefore, you should highly consider the following:

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

Breast Cancer

The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

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

Estrogens should not be taken by women who have a personal history of breast cancer.

In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT.

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

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

Overgrowth of the lining of the uterus and cancer of the uterus

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

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

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

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

Ovarian Cancer

In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

Heart Disease and Stroke

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

Abnormal Blood Clotting

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

Gallbladder Disease

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

Dementia

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in post-menopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

BEFORE you use pms-Estradiol Valerate Injection talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and or/breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease or liver tumours, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headaches
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)

• have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
• have been diagnosed with diabetes
• have been diagnosed with porphyria (a disease of blood pigment)
• have a history of high cholesterol or high triglycerides
• are pregnant or may be pregnant
• have had a hysterectomy (surgical removal of the uterus)
• smoke
• are breast feeding
• have a history of endometrial hyperplasia (overgrowth of the lining of the uterus)
• have had partial or complete loss of vision due to blood vessel disease of the eye
• have a history of a psychiatric condition (including depression)
• have been told that you have a condition called hereditary angioedema or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract.
• have been diagnosed with lupus
• have been diagnosed with hearing loss due to otosclerosis

INTERACTIONS WITH THIS MEDICATION

INTERACTIONS WITH THIS MEDICATION
Some medications can interfere with the action of pms-ESTRADIOL VALERATE INJECTION and pms-ESTRADIOL VALERATE INJECTION can interfere with the action of other medications. When you are taking pms-ESTRADIOL VALERATE INJECTION it is important to let your physician know if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins and herbal products.
It is especially important to let your doctor know if you are taking any of the following:
• anticoagulant (anti-blood clotting) medications
• diabetic medications
• blood pressure medications
• barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone, rifampicin
• herbal products such as St. John's Wort
Some drug interactions are also suspected with the following medications: phenobarbital, phenytoin, ascorbic acid, acetaminophen, cyclosporine, prednisolone, theophylline, temazepam, salicylic acid, morphine, clofibric acid and atorvastatin.

PROPER USE OF THIS MEDICATION

Usual dose:
pms-ESTRADIOL VALERATE INJECTION is administered by intramuscular injection. pms-ESTRADIOL VALERATE INJECTION should only be used under a physician's supervision. The dosage, frequency and duration of your treatment with pms-ESTRADIOL VALERATE INJECTION should be based on the reason for use, as carefully determined by your physician.
You and your physician should talk regularly about whether you still need treatment with estrogen.

For women:

Cyclic Therapy Schedule (28-day cycle; repeated every 4 weeks)
Day 1 of each cycle: 20 mg pms-ESTRADIOL VALERATE INJECTION
2 weeks after Day 1: 5 mg pms-ESTRADIOL VALEREATE INJECTION
4 weeks after Day 1: This is Day 1 of next cycle.

Amenorrhea primary and secondary (the suppression or unusual absence of menstruation)
See Cyclic Therapy Schedule. Repeat every 4 weeks. Stop after 4 cycles.

Deficiency Syndroms (castration, primary ovarian failure, menopause)
See Cyclic Therapy Schedule: Start therapy any time. Repeat every 4 weeks. Stop after 4 cycles.

Local Manifestations (signs and indications) of Estrogen Deficiency (senile vaginitis, pruritus vulvae)
See Cyclic Therapy Schedule: Start therapy any time. Repeat every 4 weeks. Stop after 4 cycles.

For men:

(For palliation only – reduce the intensity only)
inoperable progressing prostatic carcinoma (prostate cancer)

30 mg or more every 1 to 2 weeks. Schedule and duration of treatment should be determined by the treating physician. Close medical supervision is mandatory.

Overdose:

In case of overdosage or ingestion of pms-Estradiol Valerate Injection, contact your physician or local

poison control centre.

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

Over dosage with pms-ESTRADIOL VALERATE INJECTION may cause nausea, vomiting, abdominal cramps, headache, dizziness, breast discomfort, vaginal bleeding, water retention, bloating and general malaise (general feeling of discomfort or feeling unwell).

Missed Dose:
If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All medicines can have side effects. Sometimes they are serious, most of the time they are not. Check with your doctor as soon as possible if any of the following occur: swelling ankles, fingers or abdomen due to fluid retention (oedema) persisting for more than 6 weeks, change in weight, change in your sex drive, change in vaginal discharge (may be a sign that too much estrogen is taken), vaginal thrush (vaginal fungal infection with severe itching, vaginal discharge), hair loss, excessive hairiness, spotty darkening of the skin, particularly on the face or abdomen (chloasma), rash, itching, acne, dryness or discoloration of the skin, purple skin patches, contact lens discomfort. It may be irritating at the site of injection.

In males, the most common side effects are gynecomastia (breast enlargement) and soreness of breast, reduced potency and feminization. Hypercalcemia may develop.

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

Frequency (common or uncommon)	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Painful and/or heavy periods		√	
	Intolerable breast tenderness			√
	Decline of memory or mental ability			√
Common	Breast lump, unusual discharge.		√	
	Pain or swelling in the leg.			√
	Unexpected vaginal bleeding.		√	
Uncommon	Abdominal pain, nausea or vomiting		√	
	Persistent sad mood			√

Rare	Unusual fatigue, cold sweat, sleep disturbance, indigestion, anxiety		√	
	Sharp pain in the chest, coughing blood or sudden shortness of breath			√
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			√
	Crushing chest pain or chest heaviness			√
Very rare	Sudden partial or complete loss of vision			√
	Yellowing of the skin or eyes			√

This is not a complete list of side effects. If you have any unexpected effects while taking this drug, contact your doctor or pharmacist.

HOW TO STORE IT

Store the vials between 15°C and 30°C. Low temperatures may result in separation of some crystalline material, which dissolves readily on rewarming. pms-ESTRADIOL VALERATE INJECTION should not be used after the expiry date shown on the package label.

This medicine has been prescribed for your current medical problem only. Do not give it to other people.

Remember to take any unused medicine back to your pharmacist.

Keep out of reach of children.

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 0701C
  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 side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Pharmascience Inc., at 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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