PRESCRIBING INFORMATION

DELESTROGEN*
(ESTRADIOL VALERATE INJECTION, USP)

10 mg / mL

ESTROGEN

Theramed Corporation
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Control Number 084703

PRESCRIBING INFORMATION

DELESTROGEN *
(ESTRADIOL VALERATE INJECTION, USP)

10 mg / mL

Pharmacologic Classification: ESTROGEN

Warning:

As the Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep venous thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens and medroxyprogesterone acetate compared to those receiving placebo tablets, the following should be highly considered:

- 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 recognized indication.

ACTION AND CLINICAL PHARMACOLOGY

DESCRIPTION

DELESTROGEN (Estradiol Valerate Injection, USP) is a long-acting sterile preparation containing the valeric acid ester of naturally occurring estradiol in sesame oil solution for intramuscular use.

ACTIONS

DELESTROGEN has a prolonged estrogenic action lasting approximately two to three weeks after a single intramuscular injection. A single injection of DELESTROGEN provides a continuous supply of estrogen closely resembling the pattern of estrogen produced by the normal ovary.

DELESTROGEN promotes the growth of the endometrium; promotes thickening, stratification, and cornification of the vagina; causes growth of mammary gland ducts; and inhibits the anterior pituitary gland.

Clinical Pharmacology of Estrogen

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

Estrogens are important in 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. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. 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. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone – especially in its sulfate ester form – is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

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.

DELESTROGEN has a prolonged estrogenic action lasting approximately two to three weeks after a single intramuscular injection. A single injection of DELESTROGEN provides a continuous supply of estrogen closely resembling the pattern of estrogen produced by the normal ovary.
(See **Therapy Guide** for dosage details.)

Pharmacokinetics of DELESTROGEN

After oral or parenteral administration, estradiol valerate, the synthesis compound, is completely converted into the natural substances **17β-estradiol** and **valeric acid**. The **17β-estradiol** produced on cleavage of the ester behaves in the organism like the endogenous steroid hormone. Estradiol valerate and 17β - estradiol are virtually dose-equivalent. No differences in the spectrum of action of the estrogen and its ester have been found. The pharmacokinetic behaviour and the biotransformation of the 17β-estradiol originating from estradiol valerate are no different from those of natural 17β-estradiol. Differences of practical significance exist in respect of the quantitative effect of estradiol valerate following oral and intramuscular administration.

Following intramuscular administration, DELESTROGEN (estradiol valerate) is completely released from the oily solution at the site of administration. Release of the ester takes place slowly because of increased lipophilia caused by the valeric acid, so that the desired effect is achieved. The steroid ester liberated from the depot is split by enzymatic hydrolysis into 17β - estradiol and the fatty acid. (The high plasma levels of 17β - estradiol found shortly after intravenous injection of estradiol valerate are a clear indication of very rapid cleavage of the valeric acid, which can take place not only in the liver but also in the blood and tissues.)

Because of delayed release of the steroid ester from the intramuscular depot referred to earlier the blood level does not reach its maximum for 3-5 days, after which it falls slowly, with a half-life of 4-5 days, to the 17β-estradiol concentrations measured before the treatment. A distinct increase in the 17β-estradiol level can be achieved over a period of about 14 days, with a single intramuscular injection of DELESTROGEN (estradiol valerate).

The 17β-estradiol arising in vivo from estradiol valerate behaves in the organism like endogenous 17β-estradiol and is subject to intermediate metabolism.
Estrogen drug products administrated by non-oral routes **are not subject to first-pass metabolism (**metabolic conversion that occurs primarily in the liver), but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

The metabolites of 17β-estradiol are eliminated primarily by the kidney regardless of the route of administration. One study demonstrated that, after intramuscular injection of estradiol valerate, 2.4% is retracted in the urine of women as unconjugated compounds, 89% as glucuronised substances, and 6% as sulphated substances. Of the total amount of radioactivity 2.6%was not retracted as unextractable compounds. No unchanged estradiol valerate was eliminated in the urine.

Pivotal Clinical Trials
No data available

INDICATIONS AND CLINICAL USE

DELESTROGEN is indicated in the treatment of:

- amenorrhea (primary and secondary);
- deficiency syndromes (castration, primary ovarian failure; menopause);
- local manifestation of estrogen deficiency (senile vaginitis, pruritus vulvae);
- (for palliation only) inoperable progressing prostatic carcinoma in males

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

CONTRAINDICATIONS

DELESTROGEN should not be prescribed in patients with **any of the following disorders:**

- Active hepatic dysfunction or disease, especially of the obstructive type.
- Personal history of known or suspected estrogen dependant neoplasia such as breast 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, ophthalmic vascular disease).
- Classical migraine.
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis, pulmonary embolism) or active thrombophlebitis.
- Partial or complete loss of vision due to ophthalmic vascular disease;
- Known or suspected hypersensitivity to any component of the product.

WARNINGS

See **Boxed Warnings** at the front page.

CARDIOVASCULAR DISORDERS: Available epidemiological data indicate that use of estrogen with or without progesterone is associated with an increased risk of stroke, and coronary heart disease. WHI-trial's results concluded that there are more risks than benefits among women using combined Hormone Replacement Therapy (HRT), compared to the group using placebo. In 10,000 women on combined HRT (conjugated equine estrogens / medroxyprogesterone acetate) over one year period, there were eleven more cases of coronary heart disease (37 on combined HRT versus 30 on placebo) and eight more cases of stroke (29 vs 21).

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.

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS, 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.

BREAST CANCER: Current epidemiological data indicate that the use of combined HRT is associated with an increased risk of invasive breast cancer. WHI-trial's results concluded that there are more risks than benefits among women using combined HRT (conjugated equine estrogens/medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over one year period, there were eight more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).

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 WHI trial also reported that 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.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease. 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 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 HRT (as reported in the results of WHI-trial) be discussed with the patient and weighed against its known benefits.

Regular monthly self-examination of the breasts is recommended for all women.

VENOUS THROMBOEMBOLISM: Recent epidemiological data indicate that use of estrogen with or without progesterone is associated with an increased risk of venous thromboembolism (VTE).
WHI-trial's results concluded that there are more risks than benefits among women using combined HRT (conjugated equine estrogens/medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over a period of one year, there were eighteen more cases of total blood clots in the lungs and legs (34 on combined HRT versus 16 on placebo).

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). The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major elective surgery or posttraumatic surgery, or major trauma (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). 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.

ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CARCINOMA:
The use of unopposed estrogen in women with intact uteri increases the risk of endometrial hyperplasia, which may increase the risk of endometrial cancer. The addition of a progestin to estrogen replacement therapy in women with intact uteri reduces the risk of endometrial hyperplasia (see Dosage and Administration).

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

DEMENTIA
Current epidemiological evidence indicates that the use of combined HRT is associated with a significantly increased risk of developing probable dementia. The Women's Health Initiative Memory Study, a clinical

substudy of the WHI, followed 4532 post-menopausal women age 65 and over and free of dementia at baseline. There was a reported two-fold increase in the relative risk of developing probable dementia after an average follow-up of 4.05 years in the group treated with daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone versus those treated with placebo (hazard ratio [HR] 2.05, 95% confidence interval [CI], 1.21-3.48). This increased risk would result in an additional 23 cases of dementia per 10 000 women per year (45 vs 22 per 10 000 person-years, P=0.01).

PRECAUTIONS

- Before DELESTROGEN 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 when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year and should include at least those procedures outlined above.

It is important that patients are encouraged to practice frequent self-examination of the breasts.

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

- Pre-existing uterine leiomyoma may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyoma requires discontinuation of medication.

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

- Caution is advised in patients with a history of estrogen-related jaundice and pruritus. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

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

- 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.

- Women using HRT sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT therapy may have to be discontinued.

- Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. Treatment should be stopped if there is an increase in epileptic seizures. 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.

- 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.

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

- 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 **Laboratory Tests.**

- Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

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

- The medication should be discontinued in patients with history of psychiatric abnormalities if exaggeration of symptoms occur.

- If the patient develops any sign of phlebitis or thromboembolic complications, papilledema or retinal vascular lesions, medication should be discontinued.

- Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation such as abnormal or excessive uterine bleeding, mastodynia, edema, etc.

- Estrogens may be excreted in the mother's milk and an estrogenic effect upon the nursing infant has been described.

- Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

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

DRUG INTERACTIONS

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 administrated estrogens.

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:

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

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

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

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

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

Concomitant administration of aminoglutethimide with medroxyprogesterone acetate (MPA), may significantly reduce the bioavailability of MPA.

It was found that some herbal products (e.g. St. John's wort) which are available as OTC products might affect metabolism, and therefore, efficacy and safety of estrogen/progestin products.

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

LABORATORY TESTS

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

- increased sulfobromophthalein retention;
- 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; free 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;
- reduced response to the METOPIRONE test;
- impaired glucose tolerance;
- reduced serum folate concentration;
- 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.

ADVERSE REACTIONS

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:

Gastrointestinal:
Nausea, vomiting, abdominal discomfort (cramps, pressure, pain); bloating, gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice

Genitourinary:
Breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; changes in cervical erosion and amount of cervical secretion, reactivation of endometriosis, cystitis; vaginal itching/discharge; dyspareunia; dysuria; endometrial hyperplasia; pre-menstrual-like syndrome;

Skin
Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsuitism and acne, hypersensitivity;allergic reactions and rashes, pruritus.

Endocrine
Breast swelling and tenderness; increased blood sugar levels; decreased glucose tolerance; sodium retention; in males gynecomastia, reduced potency and feminization;

Cardiovascular/Hematologic

Palpitations; isolated cases of: thrombophlebitis; thromboembolic disorders; exacerbation of varicose veins; increase in blood pressure **(see Warnings and Precautions)** in susceptible individuals.

Coronary thrombosis; altered coagulation tests **(see Laboratory Tests under Precautions)**.

Central Nervous System
Aggravation of migraine episodes; headaches; mental depression; nervousness; dizziness; fatigue; irritability, neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis).

Ophthalmic
Visual disturbances; steepening of the corneal curvature; intolerance to contact lenses; neuro-ocular lesions (see CNS above).

Miscellaneous
Changes in appetite; changes in body weight; edema; neuritis; change in libido; musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks), sterile abscess, and precipitation or aggravation of porphyria cutanea tarda in predisposed individuals may occur.

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

SYMPTOMS AND TREATMENT OF OVER DOSAGE

Symptoms: Accidental overdosage may result in nausea, vomiting, abdominal cramps, headache, dizziness, breast discomfort, bloating, vaginal bleeding and general malaise.
The transient hyperestrogenic effects may *include severe temporary sodium and water retention in some susceptible individuals.*
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.

Treatment: Treatment is symptomatic. For severe temporary sodium and water retention, consider use of diuretics when appropriate.

DOSAGE AND ADMINISTRATION:

Excluding the indication for use of DELESTROGEN in males with inoperable progressing prostatic carcinoma, malignancies that are hormone-sensitive should be ruled out before hormone therapy is started.

DELESTROGEN should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. Abnormal vaginal bleeding is an indication for prompt diagnostic measures.

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.

Care should be taken to inject DELESTROGEN deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. 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.

See **THERAPY GUIDE** for dosage details.

THERAPY GUIDE

For Women:

In general, DELESTROGEN should be administred to women cyclically.

CYCLIC THERAPY SCHEDULE (28-day cycle; repeated every 4 weeks):
Day 1 of each cycle: 20 mg DELESTROGEN (estradiol valerate injection, USP)
2 weeks after Day 1: 5 mg DELESTROGEN
4 weeks after Day 1: This is Day 1 of next cycle.

Progestin Therapy
In women with intact uteri, an appropriate dosage of a progestin should be administered for a minimum of 12 to 14 days per cycle.

Monitoring
Due to its intramuscular route of administration, estradiol blood levels following administration of DELESTROGEN 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.

SUGGESTED CYCLIC REGIMEN

INDICATIONS	DOSAGE	START	REPEAT	STOP	COMMENTS
Amenorrhea (primary and secondary)	See Cyclic Therapy Schedule	After excluding a diagnosis of early pregnancy or endometrial pathology on the basis of presenting symptomatology	Every 4 weeks	After 4 cycles	To determine onset of normal cyclic function, patient should be observed for 2 to 3 cycles after cessation of therapy
Deficiency syndromes (castration; primary ovarian failure; menopause)	See Cyclic Therapy Schedule	Any time	Every 4 weeks	After 4 cycles	----
Local manifestations of estrogen deficiency (senile vaginitis; pruritus vulvae)	See Cyclic Therapy Schedule	Any time	Every 4 weeks	After 4 cycles	----

For Men:

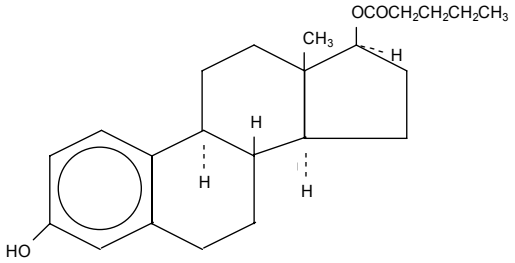
SUGGESTED NON-CYCLIC REGIMEN

INDICATIONS	DOSAGE	START	REPEAT	STOP	COMMENTS	

(For palliation only) Inoperable progressing prostatic carcinoma in males)	30 mg or more DELESTROGEN	Any time	Every 1 to 2 weeks	----	Close medical supervision is mandatory. Soreness of the breasts or gynecomastia may occur; hypercalcemia may develop.

PHARMACEUTICAL INFORMATION

Chemical name: **Estra-3, 17β–diol, 17 -pentanoate**
Molecular formula: **$C_{23}H_{32}O_3$**
Structural formula: **Estradiol valerate**



Molecular weight: **356.50**

Availability: DELESTROGEN (estradiol valerate injection, USP) is available in a concentration of 10 mg/mL formulated in a sesame oil vehicle with 0.5 % chlorobutanol as a preservative; it is supplied in 5 mL vials.

Storage: DELESTROGEN should be stored at controlled room temperature (15°C- 30 °C).
Storage at low temperatures may result in the separation of some crystalline material, which re-dissolves readily on warming.

PATIENT INFORMATION

DELESTROGEN*

(ESTRADIOL VALERATE INJECTION, USP)

Please read this PATIENT INFORMATION before you start taking DELESTROGEN (estradiol valerate injection, USP) and each time you refill your prescription. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Warning:

The use of estrogens, with or without progestins, may increase your risk of developing invasive breast cancer, myocardial infarction (heart attack), stroke, deep venous thrombosis (blood clots in the leg veins) and pulmonary emboli (blood clots in the lungs).

Therefore, you should consider the following:

- Estrogens with or without progestins **should not** be prescribed to prevent heart disease or stroke.
- Estrogens with or without progestins should be prescribed at the **lowest effective dose** and for the **shortest period of time.**

INTRODUCTION: What is DELESTROGEN?

DELESTROGEN (estradiol valerate injection, USP) contains estradiol valerate, a long-acting estrogen in sterile solution for intramuscular use. These solutions are clear, colorless to pale yellow. Formulation (per mL): 10 mg estradiol valerate in vehicle containing 5 mg chlorobutanol (as preservative) and sesame oil.

DELESTROGEN should only be used under a physician's supervision. You should see your physician at least once a year while taking DELESTROGEN to identify possible adverse events associated with its use. For women, your visit may include a blood pressure check, a breast exam and a Pap smear and pelvic exam. Close medical supervision is mandatory for men when DELESTROGEN is used for the treatment of prostate cancer.
Your doctor may suggest scheduling regular mammograms (breast x-rays), and may recommend some blood tests.

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 DELESTROGEN should be based on the reason for use, as carefully determined by your physician.

DELESTROGEN is approved for use in the following situations:

- To treat **amenorrhea** (periods are absent, either periods never start or cease to occur)

- **For treatment of deficiency syndromes**
  Estrogens are hormones made by the ovaries. The ovaries normally stop making estrogens when a woman is between ages 45 and 55. This leads to a drop in body estrogen levels, which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".
  When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.

- **To treat vulval and vaginal atrophy** (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.

- **To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.**

- **To treat inoperable progressing prostatic cancer in men.**

***DELESTROGEN* 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.**

RESTRICTIONS ON USE: WHO SHOULD NOT USE DELESTROGEN

DELESTROGEN should not be used:

- If you have active liver disease.

- If you have a personal history of breast cancer or endometrial cancer (cancer of the lining of the uterus).

- If you have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus).

- If you have experienced unusual or undiagnosed vaginal bleeding. (Unusual vaginal bleeding, especially after menopause, can be a warning sign of cancer of the uterus. Your doctor should determine the cause of any unusual vaginal bleeding.)

- If you are pregnant or think you may be pregnant. (Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.)
- If you are breast-feeding.
- If you have a history of blood clots, heart attack or stroke.
- If you experience migraine headaches.
- If you have had partial or complete loss of vision due to blood vessel disease of the eye.
- If you have had an allergic or unusual reaction to any of the ingredients of DELESTROGEN (See PHARMACEUTICAL INFORMATION).

WARNINGS AND PRECAUTIONS

ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CARCINOMA:
If taken by women who have not had a hysterectomy (surgical removal of the uterus), estrogen-only hormone replacement therapy (HRT) increases the risk of endometrial hyperplasia (overgrowth of the lining of the uterus), a condition that can lead to endometrial cancer (cancer of the lining of the uterus).

Taking a progestin medication (another hormone drug) in addition to estrogen therapy lowers the risk of developing these conditions. Therefore, if you have not had a hysterectomy, your doctor will prescribe a progestin medication for you to take together with the estrogen. If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial cancer and therefore do not require the addition of a progestin medication to the estrogen therapy.

BREAST CANCER:
Recent studies indicate that the use of combined estrogen and progestin hormone replacement therapy is associated with an increased risk of developing invasive breast cancer. Women who have a family history of breast cancer, or a personal history of breast nodules, fibrocystic breast disease (breast lumps) or abnormal mammograms should consult with their doctor before starting estrogen replacement therapy.

Regular breast exams by a health professional and monthly breast self-examinations are recommended for all women.

Your doctor may recommend that you have a mammogram (breast x-ray) before starting hormone replacement therapy and at regular intervals during treatment.

VENOUS THROMBOEMBOLISM (*blood clots in the veins):*
Taking estrogens may cause changes in your blood clotting system. Hormone replacement therapy has been associated with an increased risk of venous thromboembolism (blood clots in the veins) and pulmonary embolism (blood clots in the lung). These conditions can cause death or serious long-term health problems.

Other risk factors for venous thromboembolism include: a personal history of blood clots, a family history of blood clots, severe obesity, age, smoking and varicose veins. The risk of blood clots is temporarily increased if you remain immobilized for long periods of time, following serious injuries and following certain types of surgery.

CARDIOVASCULAR DISORDERS:
Use of estrogen with or without progestin is associated with an increased risk of heart disease and stroke. Women using HRT sometimes experience increased blood pressure.

GALLBLADDER DISEASES:
Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than those who do not use estrogens.

DEMENTIA:

Current studies indicate that the use of combined estrogen and progestin in women age 65 and over may increase the risk of developing probable dementia (loss of memory and intellectual function).

ADVERSE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Abnormal vaginal bleeding
- Headache
- Breast tenderness or enlargement.
- Retention of excess fluid. This may worsen some conditions, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- Nausea and vomiting.
- Enlargement of benign tumors ("fibroids") of the uterus.

These are not all of the possible side effects of estrogen use. For more information you should speak with your healthcare provider.

Be alert of signs of trouble – if any of these warning signs (or any other unusual symptoms) happen while using estrogens, call your doctor immediately:

- Abnormal vaginal bleeding (possible uterine cancer)
- Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
- Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)
- Breast lumps (possible breast cancer)
- Yellowing of the skin or eyes (possible liver problem)
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

HOW TO USE

DELESTROGEN is a preparation for intramuscular use. DELESTROGEN should only be used under a physician's supervision. The dosage, frequency (how often), and duration of your treatment with DELESTROGEN should be based on the reason for use, as carefully determined by your physician.

Some medications can interfere with the action of DELESTROGEN and DELESTROGEN can interfere with the action of other medications. When you are taking DELESTROGEN it is especially important to let your physician know if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins and herbal products.

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

SYMPTOMS AND TREATMENT OF OVER DOSAGE

Symptoms: Over dosage with DELESTROGEN may cause nausea, vomiting, abdominal cramps, headache, dizziness, breast discomfort, fluid retention, bloating or vaginal bleeding.
Treatment: Contact your physician or your local Poison Control Centre in case of accidental over dosage or ingestion of DELESTROGEN.

PHARMACEUTICAL INFORMATION

Availability: DELESTROGEN (estradiol valarete injection, USP) is a long-acting sterile preparation for intramuscular use. It is available in a concentration of 10 mg/mL formulated in a sesame oil vehicle with 0.5 % chlorobutanol as a preservative; it is supplied in 5 mL vials.

STORAGE

DELESTROGEN should be stored at controlled room temperature (15°C- 30°C).
Storage at low temperatures may result in the separation of some crystalline material, which re-dissolves readily on warming.

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