MEDROXYPROGESTERONE AND ESTRADIOL (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾ HS104

Commonly used brand name(s):Lunelle.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Contraceptive, systemic .

Indications

Accepted

Pregnancy, prevention of¾The combination of estradiol and medroxyprogesterone in a monthly contraceptive injection is indicated for the prevention of pregnancy. 1

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾Medroxyprogesterone acetate: 386.53 1

Estradiol cypionate: 396.57 1

Mechanism of action/Effect:

The combination of medroxyprogesterone and estradiol inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation.
Other possible mechanisms include thickening and reduction in volume of cervical mucus, which decreases sperm penetration and also endometrial thinning which leads to a reduction in the likelihood of implantation. 1

Absorption:

Medroxyprogesterone and estradiol absorption is prolonged after an intramuscular injection 1

Protein binding:

Medroxyprogesterone acetate¾High (86%); Binds primarily to serum albumin, and no binding occurs with sex-hormone-binding globulin (SHBG) 1

Estradiol¾High (97%); Binds primarily to sex-hormone-binding globulin (SHBG) and albumin. Also binds to a-1-glycoproteins and transcortin. 1

Biotransformation:

Medroxyprogesterone acetate¾Metabolism primarily involves ring A or side-chain reductions, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21- positions or a combination of the positions; result is numerous derivatives. 1

Estradiol cypionate¾Undergoes ester hydrolysis and releases the parent, active compound 17{\f23 b}-estradiol (E2). E2is primarily metabolized into estrone and estriol, which are metabolized into their sulfate and glucuronide forms. 1

Half-life:

Medroxyprogesterone acetate¾Elimination: 15 days 1

17{\f23 b}-estradiol (E2)¾Elimination: 7-8 days 1

Time to peak concentration:

Medroxyprogesterone acetate¾1 to 10 days post injection 1

17{\f23 b}-estradiol (E2)¾ 1 to 7 days post injection 1

Peak serum concentration:

Medroxyprogesterone acetate¾1.25 ng/mL (mean Cmax) 1

17{\f23 b}-estradiol (E2)¾0.25 ng/mL (mean Cmax) 1

Precautions to Consider

Carcinogenicity

No long term studies have been done with the combination of medroxyprogesterone and estradiol to evaluate the risk of carcinoma of the female reproductive organs. 1

Numerous epidemiological studies have been done on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. In spite of the many studies that have been done on the relationship between oral contraceptive use and breast and cervical cancers, a cause and effect relationship has not been established. 1

Tumorigenicity

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of these is rare in the United States. The risk increases after 4 or more years of use. These benign hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. 1

Mutagenicity

Clinical studies do not suggest an increased risk of mutagenicity or teratogenicity, including any development of fetal cardiac anormalies and limb reduction defects, when oral contraceptives are inadvertently taken during early pregnancy. 1

Pregnancy/Reproduction

Fertility¾Return of ovulation and fertility was observed 63 to 112 days post treatment in 11 out of the 14 women participating in a study who received three monthly injections. 1

Another study showed that 52% of the women ovulated during the first post-treatment month, and 72% during the second post-treatment month. 1

Pregnancy¾The use of the combination of medroxyprogesterone and estradiol is contraindicated during pregnancy. 1

No long term studies have been done with the combination of medroxyprogesterone and estradiol, but studies have been done with combination oral contraceptives. These studies have shown that combination oral contraceptives do not appear to increase the risk of birth defects when they are used before pregnancy. Studies have also shown that oral contraceptives, when taken inadvertently during early pregnancy, do not seem to have a teratogenic effect. 1

Unexpected pregnancies in women who receive medroxyprogesterone and estradiol are uncommon, and have not shown congenital malformations or other adverse events. 1

Any patient who has missed two consecutive menstrual periods or if the injection interval was not followed the patient should not be administered another injection until it has been determined that there is no possibility of pregnancy. 1

FDA Pregnancy Category X. 1

Breast-feeding

It is not known whether medroxyprogesterone and estradiol combination is distributed into the breast milk. However, nursing mothers who have been administered estrogen have shown to have a decreased quantity and quality of breast milk. Small amounts of combined hormonal contraceptive steroids have been detected in the breast milk of nursing mothers and a few adverse effects on their children have been reported, such as jaundice and breast enlargement. 1

Long term follow up of children whose mothers used a combined hormonal contraceptive while breast feeding have shown no deleterious effects. 1

It is recommended that nursing mothers should not start taking combined hormonal contraceptives until six weeks post partum. 1

Pediatrics

No information is available on the relationship of age to the effects of the combination of medroxyprogesterone and estradiol in the pediatric population. Safety and efficacy have not been established.

Adolescents

Although appropriate studies on the relationship of age to the effects of medroxyprogesterone and estradiol combination have not been performed in the adolescent population, safety and efficacy are expected to be the same for postpubertal adolescents under 16 years of age and users older than 16 years. Use of medroxyprogesterone and estradiol is not indicated prior to menarche. 1

Geriatrics

No information is available on the relationship of age to the effects of the combination of medroxyprogesterone and estradiol in geriatric patients. Safety and efficacy have not been established.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Acetaminophen or

Ascorbic acid

(concurrent use may increase plasma concentrations of some synthetic estrogens, possibly by the inhibition of conjugation. 1)

>> Aminoglutethamide

(may decrease the serum concentration of medroxyprogesterone thus decreasing contraceptive efficacy 1)

>> Carbamazepine or

>> Phenobarbital or

>> Phenytoin

(concurrent use has been shown to increase the metabolism of some synthetic estrogens and progestins, which could result in decreased contraceptive efficacy 1)

Phenylbutazone

(concurrent use may result in a reduction in contraceptive effectiveness and an increased incidence of menstrual irregularities 1)

>> Rifampin

(concurrent use may cause increased metabolism of some synthetic estrogens and progestins, possibly resulting in decreased contraceptive efficacy and menstrual irregularities 1)

St. John's Wort (hypericum perforatum)

(concurrent use may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce effectiveness and may cause breakthrough bleeding 1)

Note: Combined hormonal contraceptives containing some synthetic estrogens may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline has been reported with concomitant use. 1

Combined hormonal contraceptives may also induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance of clofibric acid, morphine, salicylic acid, and temazepam have been noted when these drugs were administered concomitantly. 1

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Endocrine and liver function tests and blood components

Antithrombin 3

(decreased) 1

Norepinephrine-induced platelet aggregability

(increased) 1

Clotting factors VII, VIII, IX, and X or

Prothrombin

(increased 1)

Sex hormone-binding globulin (SHBG), serum or

Thyroid-binding globulin (TBG) or

Triglycerides

(SHBG and TBG are increased by combined hormonal contraceptives. The serum concentrations of total sex steroids and corticoids also increase, but free or biologically active levels remain unchanged. The total thyroid hormone also increases, but free thyroid concentration is unchanged 1)
(triglycerides may be increased by combined hormonal contraceptives 1)

Thyroid function tests

Thyroxine (T4) determinations

(the amount of T4 that is protein bound, which is measured by column or by radioimmunoassay, elevates because of increased thyroid binding globulin [TBG]; serum free T4 concentrations are unchanged 1)

Triiodothyronine (T3) determinations

(T3resin uptake is decreased because of increased TBG 1)

With physiology/laboratory test values

Folic acid, serum or

Glucose, plasma or serum

(glucose tolerance may be decreased by combined hormonal contraceptives. Serum folate levels may be depressed, which may be clinically significant if a woman becomes pregnant shortly after discontinuing combined hormonal contraceptive therapy 1)

The following tests may be affected by progestins

Cortisol or

Estradiol or

Pregnanediol or

Progesterone or

Testosterone

(plasma and urinary steroid levels are decreased 1)

Gonadotropins

(levels may be decreased) 1

Sex hormone-binding globulin

(concentrations are decreased) 1

Note: Pathologists should be advised of combined hormonal contraceptive therapy when relevant tissue samples are submitted. 1

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Carcinoma, breast, known or suspected

>> Carcinoma, endometrium

>> Neoplasia, estrogen-dependent, known or suspected

(use of estrogen-containing contraceptives may worsen condition and should be discontinued) 1

>> Cerebrovascular disease, active or history of or

>> Coronary artery disease, active or history of

(oral contraceptives have been shown to increase the risk of cerebrovascular events, and overall the greatest risk is in women who are over 35 years old, hypertensive and smoke 1)
(an increased risk of myocardial infarction has been associated with the use of oral contraceptives, which is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. A substantially increased incidence of myocardial infarction and mortality rates associated with circulatory disease has been shown in women over 35 years of age or older with smoking) 1

>> Hepatic disease, cholestatic, active, or history of

>> Hepatic tumors, benign or malignant, or history of

(condition may be worsen and use of estrogen-containing contraceptives should be discontinued 1)

>> Thrombophlebitis, thrombosis, or thromboembolic disorders, active or history of

(increased risk in women using oral contraceptives is well established; if any occur or are suspected then the combination of medroxyprogesterone and estradiol should not be readministered) 1

>> Uterine bleeding, abnormal or undiagnosed

(persistent or severe bleeding should be investigated to rule out the possibility of organic pathology; in the event of amenorrhea pregnancy should be ruled out 1)

Risk-benefit should be considered when the following medical problems exist

Diabetes with vascular involvement 1

Emotional disorders

(patients who become significantly depressed while taking combined hormonal contraceptives should stop the medication and change to another method of contraception to determine if the condition is drug related; women who have a history of depression should be carefully observed; if depression recurs then discontinuation should be considered) 1

Gallbladder disease, or history of, especially gallstones

(combined hormonal contraceptives may worsen existing disease, and may accelerate the development of this disease in previously asymptomatic women; women with a history of combined hormonal contraceptive-related cholestasis are more likely to have the condition reoccur with subsequent combined hormonal contraceptive use) 1

Headaches

(focal neurological symptoms or migraine headaches that are recurrent, persistent or severe require evaluation of cause before further injections are given) 1

Hypersensitivity to any of the ingredients contained in the medroxyprogesterone and estradiol combination injection 1

>> Hypertension

(increase in blood pressure has been observed, and is more likely in older patients with continued use) 1

Liver dysfunction

(steroid hormones may be poorly metabolized in patients with impaired liver function, resulting in a worsening of the condition; therefore, combined hormonal contraceptives should be discontinued) 1

Lipid Disorders

(patients being treated for hyperlipidemias should be followed closely as some progestins will elevate LDL levels and may make hyperlipidemias more difficult to control) 1

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Hepatic function determinations and

>> Physical examination

(the physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests 1)
(women with a family history of breast cancer or who have breast nodules should be monitored carefully) 1

(special attention to rule out malignancy should be given to patients complaining of persistent or recurrent abnormal uterine bleeding 1)

Lipid profile, serum and

Lipoprotein profile, serum

(needed for patients who are being treated for hyperlipidemias 1)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Note: Increased risk of arterial thromboembolism, cerebral hemorrhage or thrombosis, gallbladder disease, hepatic adenomas or benign liver tumors, hypertension, myocardial infarction, pulmonary embolism, and thrombophlebitis has been associated with the use of combined hormonal contraceptives. 1

Those indicating need for medical attention

Incidence more frequent

Anaphylactic reactions 1 (cough ; difficulty swallowing; dizziness; fast heartbeat; hives; itching ; puffiness or swelling of the eyelids or around the eyes, face, lips or tongue ; shortness of breath ; skin rash; tightness in chest ; unusual tiredness or weakness ; wheezing) 1; cholestatic jaundice 1 (loss of appetite; nausea ; rash ; unpleasant breath odor; unusual tiredness or weakness ; vomiting of blood ; yellow eyes or skin); corneal curvature changes 1¾ i.e. steepening; edema 1 (decreased urination ; rapid weight gain ; bloating or swelling of face, hands, lower legs, and/or feet)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal pain 1; acne 1; alopecia 1 (hair loss ; thinning of hair); amenorrhea 1 (stopping of menstrual bleeding over several months); asthenia 1 (lack or loss of strength); breast

tenderness/pain 1; decreased libido; depression; decrease in lactation when given immediately postpartum 1; dizziness 1; dysmenorrhea 1; emotional lability 1 (crying; depersonalization ; dysphoria ; euphoria; mental depression; paranoia; quick to react or overreact emotionally ; rapidly changing moods); enlarged abdomen 1; headache 1; melasma 1 (brown, blotchy spots on exposed skin); menorrhagia 1 (increased amount of menstrual bleeding occurring at regular monthly periods); metrorrhagia 1 (normal menstrual bleeding occurring earlier, possibly lasting longer than expected); nausea 1; nervousness 1; rash, allergic 1; reduced carbohydrate tolerance 1; vaginal moniliasis 1 (vaginal yeast infection); vulvovaginal disorder 1; weight change 1

Overdose

For more information on the management of overdose or unintentional ingestion, contact a poison control center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Nausea 1; menstrual irregularities 1; vaginal bleeding 1; vomiting 1

Treatment of overdose

There is no known specific antidote to medroxyprogesterone and estradiol combination. Treatment is generally symptomatic and supportive. 1

Supportive care¾
Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Medroxyprogesterone and Estradiol (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Hypersensitivity to estrogens or progestins
Pregnancy¾Not indicated for use during pregnancy
Breast-feeding¾Combined hormonal contraceptives are distributed into breast milk. Not recommended to start taking combined hormonal contraceptives until six weeks postpartum
Use in adolescents¾Careful counseling may be required to increase compliance
Other medications, especially aminoglutethamide, carbamazepine, phenobarbital, phenytoin, or rifampin

Other medical problems, especially carcinoma of the reproductive organs or breasts, cerebrovascular disease, coronary artery disease, genital bleeding that is abnormal or undiagnosed, hypertension, and thrombophlebitis, thrombosis, or thromboembolic disorders
Proper use of this medication

>> Proper dosing
If dose exceeds 33 days then pregnancy must be ruled out before another injection is given
Precautions while using this medication

>> Regular visits to physician every 12 months to check progress and have a physical exam

No protection of transmission of human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) and other sexually transmitted diseases (STDs)

Side/adverse effects

Signs of potential side effects, especially anaphylactic reactions, cholestatic jaundice, corneal curvature changes and edema

General Dosing Information

The first injection should be given within the first 5 days of the onset of a normal menstrual period or within 5 days of a complete first trimester abortion. 1

The first injection for postpartum administration should be given no earlier than 4 weeks if patient is not breast-feeding, and no earlier than 6 weeks if patient is breast-feeding. 1

The second injection should be monthly (every 28 to 30 days) not to exceed 33 days. If the patient has exceeded the prescribed schedule then pregnancy should be considered, and should be ruled out before another injection is given. 1

Do not shorten the injection interval, as this could lead to a change in the patient's menstrual pattern. 1

Do not use bleeding episodes to guide the injection schedule. 1

When switching from other methods of contraception the injection should be given in manner that continuous contraceptive coverage is insured, based on the mechanism of action of both methods. 1

Patients should be counseled that this contraceptive does not provide protection against HIV Infection (AIDS) and other sexually transmitted diseases. 1

Parenteral Dosage Forms

MEDROXYPROGESTERONE AND ESTRADIOL FOR INJECTION

Usual Adult Dose

Contraceptive¾
Intramuscular, 0.5 mL, into the deltoid, gluteus maximus, or anterior thigh, once a month (every 28 to 30 days). 1

Usual Pediatric Dose

Safety and efficacy have not been established. 1

Usual Geriatric Dose

Safety and efficacy have not been established. 1

Strength(s) usually available
U.S.¾25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate (Rx)[Lunelle (monthly contraceptive injection) (methylparaben (0.9 mg)) (polyethylene glycol (14.28 mg)) (polysorbate 80 (0.95 mg)) (propylparaben (0.1 mg)) (sodium chloride (4.28 mg))] 1

Packaging and storage:

Store at 25 °C (77 °F), excursions permitted to 15 °C- 30 °C (59-86 °F). 1

Preparation of dosage form:

Should be shaken vigorously before administration. 1

Auxiliary labeling:

· Shake well. 1