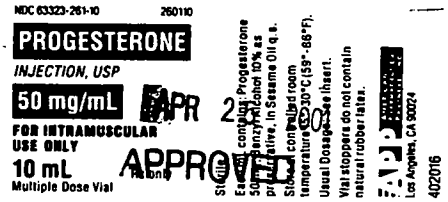
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-906

APPROVED DRAFT LABELING

Final Printed Vial



7H

PROGESTERONE
INJECTION, USP
50 mg/mL

Sterile
Each mL contains: Progesterone 50 mg, Benzyl Alcohol 10% as preservative, in Sesame Oil q.s.
Usual Dosage: See insert.
Vial stoppers do not contain natural rubber latex.

Store at controlled room temperature 15°-30°C (59°-86°F).

PHYSICIAN: Patient literature must be provided to premenopausal women except those in whom childbearing is impossible.

APR 25 2001
APPROVED

AMERICAN PHARMACEUTICAL PARTNERS INC
Los Angeles, CA 90024

NDC 63323-261-10 260110

PROGESTERONE

INJECTION, USP

50 mg/mL

FOR INTRAMUSCULAR USE ONLY

10 mL Multiple Dose Vial

Rx only

AMERICAN PHARMACEUTICAL PARTNERS INC

N 3 63323-261-10 8

62742

BLACK 226C

Vial stoppers do not contain natural rubber latex.

Store at controlled room temperature 15°-30°C (59°-86°F).

PATIENT INFORMATION:
This is a progestational drug. The information below is required by the U.S. Food and Drug Administration to be provided to all patients taking such products. This information relates only to the risk to the unborn child associated with use of progestational drugs during pregnancy. For further information on the use, side effects, and other risks associated with this product, ask your doctor.

WARNING FOR WOMEN:
Progesterone or progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Furthermore, most cases of early miscarriage are due to causes which could not be helped by these drugs.

There is an increased risk of minor birth defects in children whose mothers take this drug during the first 4 months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies.

The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5 to 8 per 1,000 male births and is about doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses, but enlargement of the clitoris and fusion of the labia may occur, although rarely.

Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy.

These drugs have been used as a test for pregnancy but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available.

If you take progesterone or a progesterone-like drug and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024
45918
Issued: January 2001

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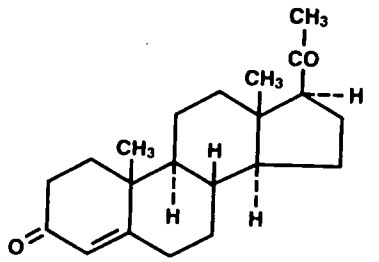
PROGESTERONE
INJECTION, USP
IN SESAME OIL
FOR INTRAMUSCULAR USE ONLY

DESCRIPTION:
Progesterone injection, a progestin, is a sterile solution of progesterone in a suitable vegetable oil available for intramuscular use.

Progesterone occurs as a white or creamy white, crystalline powder. It is odorless and is stable in air. Practically insoluble in water, it is soluble in alcohol, acetone, and dioxane and sparingly soluble in vegetable oils.

It has the following structural formula:



$C_{21}H_{30}O_2$ M.W. 314.47
Pregn-4-ene-3, 20-dione

Each mL contains: Progesterone 50 mg, Benzyl Alcohol 10% as preservative in Sesame Oil q.s.

CLINICAL PHARMACOLOGY:
Transforms proliferative endometrium into secretory endometrium.

Inhibits (at the usual dose range) the secretion of pituitary gonadotropins, which in turn prevents follicular maturation and ovulation.

May also demonstrate some estrogenic, anabolic, or androgenic activity but should not be relied upon.

INDICATIONS AND USAGE:
This drug is indicated in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.

CONTRAINDICATIONS:
1. Current or past history of thrombophlebitis, thromboembolic disorders, or cerebral apoplexy.
2. Liver dysfunction or disease.
3. Known or suspected malignancy of breast or genital organs.
4. Undiagnosed vaginal bleeding.
5. Missed abortion.
6. As a diagnostic test for pregnancy.
7. Known sensitivity to progesterone injection.

WARNINGS:
The use of progestational drugs during the first four months of pregnancy is not recommended. Progestational agents have been used beginning with the first trimester of pregnancy in attempts to prevent abortion but there is no evi-

dence that such use is effective. Furthermore, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1,000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as some of these-drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Medication should be discontinued pending examination if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Detectable amounts of drug have been identified in the milk of mothers receiving progestational drugs. The effect of this on the nursing infant has not been determined.

PRECAUTIONS:

General

The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear.

Because progestational drugs may cause some degree of fluid retention, conditions which might be influenced by this condition, such as epilepsy, migraine, asthma, cardiac, or renal dysfunction, require careful observation.

In cases of breakthrough bleeding, as in all cases of irregular bleeding *per vaginum*, nonfunctional causes should be borne in mind, and adequate diagnostic measures undertaken.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

The age of the patient constitutes no absolute limiting factor although treatment with progestin may mask the onset of the climacteric.

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

There are possible risks which may be associated with the use of progestin treatment, including adverse effects on carbohydrate and lipid metabolism. The dosage used may be important in minimizing these adverse effects.

A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination treatment. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving such therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term intramuscular administration of Medroxyprogesterone acetate (MPA) has been shown to produce mammary tumors in beagle dogs. There is no evidence of a carcinogenic effect associated with the oral administration of MPA to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

Progesterone at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

Information for the Patient

See Patient information at end of insert.

ADVERSE REACTIONS:

(See **WARNINGS** for possible adverse effects on the fetus.) Breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; edema; change in weight (increase or decrease); changes in cervical erosion and cervical secretions; cholestatic jaundice; breast tenderness and galactorrhea; skin sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash; acne, alopecia and hirsutism; rash (allergic) with and without pruritus; anaphylactoid reactions; mental depression; pyrexia; insomnia; nausea; and somnolence.

A statistically significant association has been demonstrated between use of estrogen-progestin combination drugs and pulmonary embolism and cerebral thrombosis and embolism. For this reason patients on progestin therapy should be carefully observed. There is also evidence suggestive of an association with neuro-ocular lesions, eg. retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs:

Rise in blood pressure in susceptible individual, premenstrual syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, and dizziness.

The following laboratory results may be altered by the use of estrogen-progestin combination drugs: increased sulfobromophthalein retention and other hepatic function tests; coagulation tests: increase in prothrombin factors VII, VIII, IX, and X; metyrapone test; pregnanediol determinations; thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values.

DOSAGE AND ADMINISTRATION:

Progesterone is administered by intramuscular injection. It differs from other commonly used steroids in that it is irritating at the place of injection. This is true whether the preparation is an oil or an aqueous vehicle. The latter is particularly painful.

Amenorrhea

Five to 10 mg are given for six to eight consecutive days. If there has been sufficient ovarian activity to produce a proliferative endometrium, one can expect withdrawal bleeding 48 to 72 hours after the last injection. This may be followed by spontaneous normal cycles.

Functional Uterine Bleeding

Five to 10 mg are given daily for six doses. Bleeding may be expected to cease within six days. When estrogen is given as well, the administration of progesterone is begun after two weeks of estrogen therapy. If menstrual flow begins during the course of injections of progesterone, they are discontinued.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit.

HOW SUPPLIED:

Product No.	NDC No.	
260110	63323-261-10	Progesterone Injection, USP, 50 mg/mL, 10 mL multiple dose vial, packaged individually.

AMERICAN PHARMACEUTICAL PARTNERS, INC.

APR 25 2001

APPROVED

45919/Issued: May 2000

PATIENT LABELING FOR PROGESTATIONAL DRUG PRODUCTS

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APP AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

45919
Issued: May 2000