

Physician Information

Depo-Provera® Contraceptive Injection

medroxyprogesterone acetate
injectable suspension, USP



Pharmacia
&Upjohn



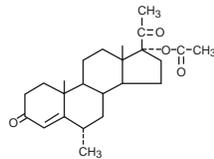
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Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

DEPO-PROVERA Contraceptive Injection contains medroxyprogesterone acetate, a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration. It is a white to off-white, odorless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6 α)-. The structural formula is as follows:



medroxyprogesterone acetate

DEPO-PROVERA Contraceptive Injection for intramuscular (IM) injection is available in vials and prefilled syringes, each containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL.

Each mL contains:

Medroxyprogesterone acetate	150 mg
Polyethylene glycol 3350	28.9 mg
Polysorbate 80	2.41 mg
Sodium chloride	8.68 mg
Methylparaben	1.37 mg
Propylparaben	0.150 mg
Water for injection	qs

When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

CLINICAL PHARMACOLOGY

DEPO-PROVERA Contraceptive Injection (medroxyprogesterone acetate), when administered at the recommended dose to women every 3 months, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. These actions produce its contraceptive effect.

Following a single 150 mg IM dose of DEPO-PROVERA Contraceptive Injection, medroxyprogesterone acetate concentrations, measured by an extracted radioimmunoassay procedure, increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 to 200 days following injection. Using an unextracted radioimmunoassay procedure for the assay of medroxyprogesterone acetate in serum, the apparent half-life for medroxyprogesterone acetate following IM administration of DEPO-PROVERA Contraceptive Injection is approximately 50 days.

Women with lower body weights conceive sooner than women with higher body weights after discontinuing DEPO-PROVERA Contraceptive Injection.

The effect of hepatic and/or renal disease on the pharmacokinetics of DEPO-PROVERA Contraceptive Injection is unknown.

INDICATIONS AND USAGE

DEPO-PROVERA Contraceptive Injection is indicated only for the prevention of pregnancy. To ensure that DEPO-PROVERA Contraceptive Injection is not admin-

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istered inadvertently to a pregnant woman, the first injection must be given **ONLY** during the first 5 days of a normal menstrual period; **ONLY** within the first 5-days postpartum if not breast-feeding, and if exclusively breast-feeding, **ONLY** at the sixth postpartum week. The efficacy of DEPO-PROVERA Contraceptive Injection depends on adherence to the recommended dosage schedule (see DOSAGE AND ADMINISTRATION). It is a long-term injectable contraceptive in women when administered at 3-month (13-week) intervals. Dosage does not need to be adjusted for body weight.

In five clinical studies using DEPO-PROVERA Contraceptive Injection, the 12-month failure rate for the group of women treated with DEPO-PROVERA Contraceptive Injection was zero (no pregnancies reported) to 0.7 by Life-Table method. Pregnancy rates with contraceptive measures are typically reported for only the first year of use as shown in Table 1. Except for intrauterine devices (IUD), implants, sterilization, and DEPO-PROVERA Contraceptive Injection, the efficacy of these contraceptive measures depends in part on the reliability of use. The effectiveness of DEPO-PROVERA Contraceptive Injection is dependent on the patient returning every 3 months (13 weeks) for reinjection.

Table 1
Lowest Expected and Typical Failure Rates*
Expressed as Percent of Women Experiencing
an Accidental Pregnancy
in the First Year of Continuous Use

Method	Lowest Expected	Typical
Injectable progestogen DEPO-PROVERA	0.3	0.3
Implants Norplant (6 capsules)	0.2†	0.2†
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15
Pill Combined Progestogen only	0.1 0.5	3
IUD Progestasert Copper T 380A	2 0.8	3
Condom	2	12
Diaphragm	6	18
Cap	6	18
Spermicides	3	21
Sponge Parous women Nulliparous women	9 6	28 18
Periodic abstinence	1-9	20
Withdrawal	4	18
No method	85	85

Source: Trussell et al¹

* Lowest expected - when used exactly as directed.

† Typical - includes those not following directions exactly.

† from Norplant® package insert.

CONTRAINDICATIONS

1. Known or suspected pregnancy or as a diagnostic test for pregnancy.
2. Undiagnosed vaginal bleeding.
3. Known or suspected malignancy of breast.
4. Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease.
5. Liver dysfunction or disease.
6. Known hypersensitivity to DEPO-PROVERA Contraceptive Injection (medroxyprogesterone acetate or any of its other ingredients).

WARNINGS

1. Bleeding Irregularities

Most women using DEPO-PROVERA Contraceptive Injection experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology, and appropriate treatment should be instituted when necessary.

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As women continue using DEPO-PROVERA Contraceptive Injection, fewer experience irregular bleeding and more experience amenorrhea. By month 12 amenorrhea was reported by 55% of women, and by month 24 amenorrhea was reported by 68% of women using DEPO-PROVERA Contraceptive Injection.²

2. Bone Mineral Density Changes

Use of DEPO-PROVERA Contraceptive Injection may be considered among the risk factors for development of osteoporosis. The rate of bone loss is greatest in the early years of use and then subsequently approaches the normal rate of age related fall.

3. Cancer Risks

Long-term case-controlled surveillance of users of DEPO-PROVERA Contraceptive Injection found slight or no increased overall risk of breast cancer³ and no overall increased risk of ovarian,⁴ liver,⁵ or cervical⁶ cancer and a prolonged, protective effect of reducing the risk of endometrial⁷ cancer in the population of users.

A pooled analysis¹⁴ from two case-control studies, the World Health Organization Study³ and the New Zealand Study¹³, reported the relative risk (RR) of breast cancer for women who had ever used DEPO-PROVERA Contraceptive Injection as 1.1 (95% confidence interval (CI) 0.97 to 1.4). Overall, there was no increase in risk with increasing duration of use of DEPO-PROVERA Contraceptive Injection. The RR of breast cancer for women of all ages who had initiated use of DEPO-PROVERA Contraceptive Injection within the previous 5 years was estimated to be 2.0 (95% CI 1.5 to 2.8).

The World Health Organization Study³, a component of the pooled analysis¹⁴ described above, showed an increased RR of 2.19 (95% CI 1.23 to 3.89) of breast cancer associated with use of DEPO-PROVERA Contraceptive Injection in women whose first exposure to drug was within the previous 4 years and who were under 35 years of age. However, the overall RR for ever-users of DEPO-PROVERA Contraceptive Injection was only 1.2 (95% CI 0.96 to 1.52).

[NOTE: A RR of 1.0 indicates neither an increased nor a decreased risk of cancer associated with the use of the drug, relative to no use of the drug. In the case of the subpopulation with a RR of 2.19, the 95% CI is fairly wide and does not include the value of 1.0, thus inferring an increased risk of breast cancer in the defined subgroup relative to nonusers. The value of 2.19 means that women whose first exposure to drug was within the previous 4 years and who are under 35 years of age have a 2.19-fold (95% CI 1.23 to 3.89-fold) increased risk of breast cancer relative to nonusers. The National Cancer Institute⁹ reports an average annual incidence rate for breast cancer for US women, all races, age 30 to 34 years of 26.7 per 100,000. A RR of 2.19, thus, increases the possible risk from 26.7 to 58.5 cases per 100,000 women. The attributable risk, thus, is 31.8 per 100,000 women per year.]

A statistically insignificant increase in RR estimates of invasive squamous-cell cervical cancer has been associated with the use of DEPO-PROVERA Contraceptive Injection in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93 to 1.70). The overall, nonsignificant relative rate of invasive squamous-cell cervical cancer in women who ever used DEPO-PROVERA Contraceptive Injection was estimated to be 1.11 (95% CI 0.96 to 1.29). No trends in risk with duration of use or times since initial or most recent exposure were observed.

4. Thromboembolic Disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, the drug should not be readministered.

5. Ocular Disorders

Medication should not be readministered 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 not be readministered.

6. Unexpected Pregnancies

To ensure that DEPO-PROVERA Contraceptive Injection is not administered inadvertently to a pregnant woman, the first injection must be given **ONLY** during the first 5 days of a normal menstrual period; **ONLY** within the first 5-days postpartum if not breast-feeding, and if exclusively breast-feeding, **ONLY** at the sixth postpartum week (see DOSAGE AND ADMINISTRATION).

Neonates from unexpected pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA Contraceptive Injection may be at an increased risk of low birth weight, which, in turn, is associated with an increased

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risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.^{9,10}

A significant increase in incidence of polysyndactyly and chromosomal anomalies was observed among infants of users of DEPO-PROVERA Contraceptive Injection, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptional exposure to DEPO-PROVERA Contraceptive Injection, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.¹¹

Neonates exposed to medroxyprogesterone acetate *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual, or social development.

Several reports suggest an association between intra-uterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (five to eight 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 because 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.

To ensure that DEPO-PROVERA Contraceptive Injection is not administered inadvertently to a pregnant woman, it is important that the first injection be given only during the first 5 days after the onset of a normal menstrual period within 5 days postpartum if not breast-feeding and if breast-feeding, at the sixth week postpartum (see DOSAGE AND ADMINISTRATION).

7. Ectopic Pregnancy

Health-care providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA Contraceptive Injection who become pregnant or complain of severe abdominal pain.

8. Lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA Contraceptive Injection. In nursing mothers treated with DEPO-PROVERA Contraceptive Injection, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to medroxyprogesterone from breast milk have been studied for developmental and behavioral effects through puberty. No adverse effects have been noted.

9. Anaphylaxis and Anaphylactoid Reaction

Anaphylaxis and anaphylactoid reaction have been reported with the use of DEPO-PROVERA Contraceptive Injection. If an anaphylactic reaction occurs appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

PRECAUTIONS

GENERAL

1. Physical Examination

It is good medical practice for all women to have annual history and physical examinations, including women using DEPO-PROVERA Contraceptive Injection. The physical examination, however, may be deferred until after initiation of DEPO-PROVERA if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. Fluid Retention

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

3. Weight Changes

There is a tendency for women to gain weight while on therapy with DEPO-PROVERA Contraceptive Injection. From an initial average body weight of 136 lb, women who completed 1 year of therapy with DEPO-PROVERA Contraceptive Injection gained an average of 5.4 lb. Women who completed 2 years of therapy gained an average of 8.1 lb.

Women who completed 4 years gained an average of 13.8 lb. Women who completed 6 years gained an average of 16.5 lb. Two percent of women withdrew from a large-scale clinical trial because of excessive weight gain.

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4. Return of Fertility

DEPO-PROVERA Contraceptive Injection has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA Contraceptive Injection to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 68% of women who do become pregnant may conceive within 12 months, 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time to conception for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-PROVERA Contraceptive Injection to become pregnant and who were lost to follow-up or changed their mind.

5. CNS Disorders and Convulsions

Patients who have a history of psychic depression should be carefully observed and the drug not be readministered if the depression recurs.

There have been a few reported cases of convulsions in patients who were treated with DEPO-PROVERA Contraceptive Injection. Association with drug use or pre-existing conditions is not clear.

6. Carbohydrate Metabolism

A decrease in glucose tolerance has been observed in some patients on DEPO-PROVERA Contraceptive Injection treatment. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving such therapy.

7. Liver Function

If jaundice develops, consideration should be given to not readministering the drug.

8. Protection Against Sexually Transmitted Diseases

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DRUG INTERACTIONS

Aminoglutethimide administered concomitantly with the DEPO-PROVERA Contraceptive Injection may significantly depress the serum concentrations of medroxyprogesterone acetate.¹² Users of DEPO-PROVERA Contraceptive Injection should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

LABORATORY TEST INTERACTIONS

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

The following laboratory tests may be affected by progestins including DEPO-PROVERA Contraceptive Injection:

- (a) Plasma and urinary steroid levels are decreased (eg, progesterone, estradiol, pregnanediol, testosterone, cortisol).
- (b) Gonadotropin levels are decreased.
- (c) Sex-hormone-binding-globulin concentrations are decreased.
- (d) Protein-bound iodine and butanol extractable protein-bound iodine may increase.
T₃-uptake values may decrease.
- (e) Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX, and X may increase.
- (f) Sulfobromophthalein and other liver function test values may be increased.
- (g) The effects of medroxyprogesterone acetate on lipid metabolism are inconsistent. Both increases and decreases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been observed in studies.

CARCINOGENESIS

See "WARNINGS" section 3.

PREGNANCY

Pregnancy Category X. See "WARNINGS" section 6.

NURSING MOTHERS

See "WARNINGS" section 8.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. See "WARNINGS" section 6.

INFORMATION FOR THE PATIENT

See Patient Labeling.

Patient labeling is included with each single-dose vial and prefilled syringe of DEPO-PROVERA Contraceptive Injection to help describe its characteristics to the patient. It is recommended that prospective users be given this labeling and be informed about the risks and benefits associated with the use of DEPO-PROVERA Contraceptive Injection, as compared with other forms

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of contraception or with no contraception at all. It is recommended that physicians or other health-care providers responsible for those patients advise them at the beginning of treatment that their menstrual cycle may be disrupted and that irregular and unpredictable bleeding or spotting results, and that this usually decreases to the point of amenorrhea as treatment with DEPO-PROVERA Contraceptive Injection continues, without other therapy being required.

ADVERSE REACTIONS

In the largest clinical trial with DEPO-PROVERA Contraceptive Injection, over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA Contraceptive Injection.

The following adverse reactions were reported by more than 5% of subjects:

Menstrual irregularities (bleeding or amenorrhea, or both)
Abdominal pain or discomfort
Weight changes
Dizziness
Headache
Asthenia (weakness or fatigue)
Nervousness

Adverse reactions reported by 1% to 5% of subjects using DEPO-PROVERA Contraceptive Injection were:

Decreased libido or anorgasmia
Pelvic pain
Backache
Breast pain
Leg cramps
No hair growth or alopecia
Depression
Bloating
Nausea
Rash
Insomnia
Edema
Leukorrhea
Hot flashes
Acne
Arthralgia
Vaginitis

Events reported by fewer than 1% of subjects included: galactorrhea, melasma, chloasma, convulsions, changes in appetite, gastrointestinal disturbances, jaundice, genitourinary infections, vaginal cysts, dyspareunia, paresthesia, chest pain, pulmonary embolus, allergic reactions, anemia, drowsiness, syncope, dyspnea and asthma, tachycardia, fever, excessive sweating and body odor, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical cancer, varicose veins, dysmenorrhea, hirsutism, unexpected pregnancy, thrombophlebitis, deep vein thrombosis.

In addition, voluntary reports have been received of anaphylaxis and anaphylactoid reaction with use of DEPO-PROVERA Contraceptive Injection.

DOSAGE AND ADMINISTRATION

Both the 1 mL vial and the 1 mL prefilled syringe of DEPO-PROVERA Contraceptive Injection should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

The recommended dose is 150 mg of DEPO-PROVERA Contraceptive Injection every 3 months (13 weeks) administered by deep, IM injection in the gluteal or deltoid muscle. To ensure the patient is not pregnant at the time of the first injection, the first injection **MUST** be given **ONLY** during the first 5 days of a normal menstrual period; **ONLY** within the first 5-days postpartum if not breast-feeding; and if exclusively breast-feeding, **ONLY** at the sixth postpartum week. If the time interval between injections is greater than 13 weeks, the physician should determine that the patient is not pregnant before administering the drug. The efficacy of DEPO-PROVERA Contraceptive Injection depends on adherence to the dosage schedule of administration.

HOW SUPPLIED

DEPO-PROVERA Contraceptive Injection (medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL) is available as:

NDC 0009-0746-30	1 mL vial
NDC 0009-0746-34	5 x 1 mL vials
NDC 0009-0746-35	25 x 1 mL vials
NDC 0009-7376-01	1 mL prefilled syringe
NDC 0009-7376-02	6 x 1 mL prefilled syringes
NDC 0009-7376-03	24 x 1 mL prefilled syringes

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Store at controlled room temperature 20° to 25°C
(68° to 77°F) [see USP].

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DEPO-PROVERA Contraceptive Injection 1 mL vials are manufactured by:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

DEPO-PROVERA Contraceptive Injection 1 mL prefilled syringes are manufactured by:
Pharmacia & Upjohn, N.V./S.A.
Puurs, Belgium

for:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

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