DEPO-PROVERA CI (medroxyprogesterone acetate) injectable suspension, for intramuscular use

Full Prescribing Information

WARNING: LOSS OF BONE MINERAL DENSITY

Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible.

It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

Depo-Provera Contraceptive Injection should not be used as a long-term birth control method (i.e., longer than 2 years) unless other birth control methods are considered inadequate *[*see *Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Depo-Provera CI is indicated only for the prevention of pregnancy. The loss of bone mineral density (BMD) in women of all ages and the impact on peak bone mass in adolescents should be considered, along with the decrease in BMD that occurs during pregnancy and/or lactation, in the risk/benefit assessment for women who use Depo-Provera CI long-term *[*see *Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Pregnancy

The 1 mL vial of Depo-Provera CI 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 CI every 3 months (13 weeks) administered by deep intramuscular (IM) injection using strict aseptic technique in the gluteal or deltoid muscle, rotating the sites with every injection. As with any IM injection, to avoid an inadvertent subcutaneous injection, body habitus should be assessed prior to each injection to determine if a longer needle is necessary particularly for gluteal IM injection.

Depo-Provera CI should not be used as a long-term birth control method (i.e., longer than 2 years) unless other birth-control methods are considered inadequate. Dosage does not need to be adjusted for body weight *[*see *Clinical Studies (12.1)]*.

To ensure the patient is not pregnant at the time of the first injection, the first injection should 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 CI depends on adherence to the dosage schedule of administration.

2.2 Switching from other Methods of Contraception

When switching from other contraceptive methods, Depo-Provera CI should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods (e.g., patients switching from oral contraceptives should have their first injection of Depo-Provera CI on the day after the last active tablet or at the latest, on the day following the final inactive tablet).

3 DOSAGE FORMS AND STRENGTHS

Sterile aqueous suspension: 150 mg/mL

4 CONTRAINDICATIONS

The use of Depo-Provera CI is contraindicated in the following conditions:

- Known or suspected pregnancy or as a diagnostic test for pregnancy.
- Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease *[*see *Warnings and Precautions (5.2)]*.
- Known or suspected malignancy of breast *[*see *Warnings and Precautions (5.3)]*.
- Known hypersensitivity to Depo-Provera CI (medroxyprogesterone acetate) or any of its other ingredients *[*see *Warnings and Precautions (5.5)]*.
- Significant liver disease *[*see *Warnings and Precautions (5.7)]*.
- Undiagnosed vaginal bleeding *[*see *Warnings and Precautions (5.10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Loss of Bone Mineral Density

Use of Depo-Provera CI reduces serum estrogen levels and is associated with significant loss of bone mineral density (BMD). This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of Depo-Provera CI by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

After discontinuing Depo-Provera CI in adolescents, mean BMD loss at total hip and femoral neck did not fully recover by 60 months (240 weeks) post-treatment *[*see *Clinical Studies (12.3)]*. Similarly, in adults, there was only partial recovery of mean BMD at total hip, femoral neck and lumbar spine towards baseline by 24 months post-treatment *[*see *Clinical Studies (12.2)]*.

Depo-Provera CI should not be used as a long-term birth control method (i.e., longer than 2 years) unless other birth control methods are considered inadequate. BMD should be evaluated when a woman needs to continue to use

Depo-Provera CI long-term. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.

Other birth control methods should be considered in the risk/benefit analysis for the use of Depo-Provera CI in women with osteoporosis risk factors. Depo-Provera CI can pose an additional risk in patients with risk factors for osteoporosis (e.g., metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, strong family history of osteoporosis or chronic use of drugs that can reduce bone mass, such as anticonvulsants or corticosteroids). Although there are no studies addressing whether calcium and Vitamin D may lessen BMD loss in women using Depo-Provera CI, all patients should have adequate calcium and Vitamin D intake.

5.2 Thromboembolic Disorders

There have been reports of serious thrombotic events in women using Depo-Provera CI (150 mg). However, Depo-Provera CI has not been causally associated with the induction of thrombotic or thromboembolic disorders. Any patient who develops thrombosis while undergoing therapy with Depo-Provera CI should discontinue treatment unless she has no other acceptable options for birth control.

Do not re-administer Depo-Provera CI 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. Do not re-administer if examination reveals papilledema or retinal vascular lesions.

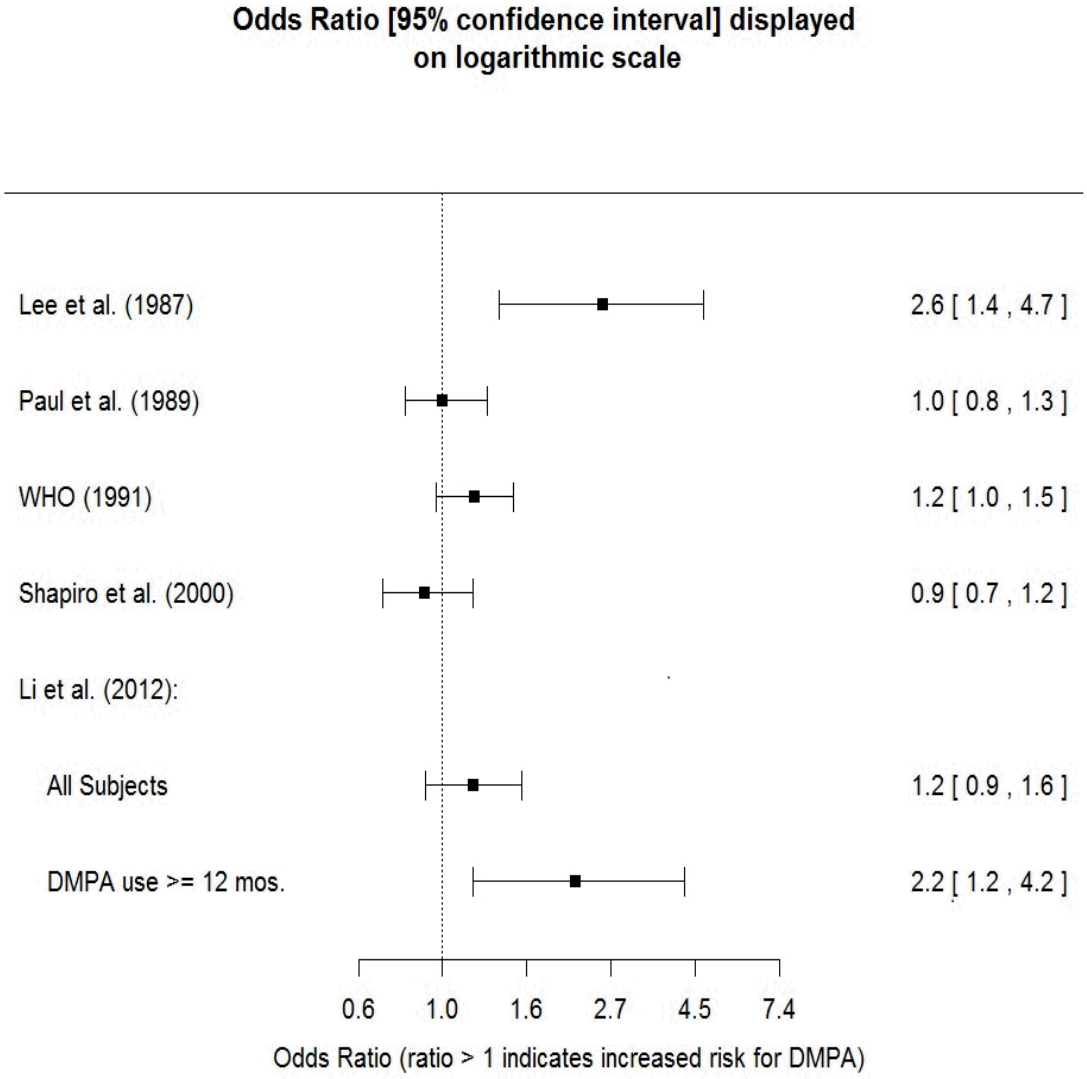
5.3 Cancer Risks

Breast Cancer

Women who have or have had a history of breast cancer should not use hormonal contraceptives, including Depo-Provera CI, because breast cancer may be hormonally sensitive *[*see *Contraindications (4)]*. Women with a strong family history of breast cancer should be monitored with particular care.

The results of five large case-control studies assessing the association between depo-medroxyprogesterone acetate (DMPA) use and the risk of breast cancer are summarized in Figure 1. Three of the studies suggest a slightly increased risk of breast cancer in the overall population of users; these increased risks were statistically significant in one study. One recent US study evaluated the recency and duration of use and found a statistically significantly increased risk of breast cancer in recent users (defined as last use within the past five years) who used DMPA for 12 months or longer; this is consistent with results of a previous study.

Figure 1 Risk estimates for breast cancer in DMPA users



Odds ratio estimates were adjusted for the following covariates:
Lee et al. (1987): age, parity, and socioeconomic status.
Paul et al. (1989): age, parity, ethnic group, and year of interview.
WHO (1991): age, center, and age at first live birth.
Shapiro et al. (2000): age, ethnic group, socioeconomic status, and any combined estrogen/progestogen oral contraceptive use.
Li et al. (2012): age, year, BMI, duration of OC use, number of full-term pregnancies, family history of breast cancer, and history of screening mammography.

Based on the published SEER-18 2011 incidence rate (age-adjusted to the 2000 US Standard Population) of breast cancer for US women, all races, age 20 to 49 years, a doubling of risk would increase the incidence of breast cancer in women who use Depo-Provera CI from about 72 to about 144 cases per 100,000 women.

Cervical Cancer
A statistically non-significant increase in RR estimates of invasive squamous-cell cervical cancer has been associated with the use of Depo-Provera CI 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, non-significant relative rate of invasive squamous-cell cervical cancer in women who ever used Depo-Provera CI 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.

Other Cancers
Long-term case-controlled surveillance of users of Depo-Provera CI found no overall increased risk of ovarian or liver cancer.

5.4 Ectopic Pregnancy
Be alert to the possibility of an ectopic pregnancy among women using Depo-Provera CI who become pregnant or complain of severe abdominal pain.

5.5 Anaphylaxis and Anaphylactoid Reaction
Anaphylaxis and anaphylactoid reaction have been reported with the use of Depo-Provera CI. Institute emergency medical treatment if an anaphylactic reaction occurs.

5.6 Injection Site Reactions
Injection site reactions have been reported with use of Depo-Provera CI *[*see *Adverse Reactions (6.2)]*. Persistent injection site reactions may occur after administration of Depo-Provera CI due to inadvertent subcutaneous administration or release of the drug into the subcutaneous space while removing the needle *[*see *Dosage and Administration (2.1)]*.

5.7 Liver Function
Discontinue Depo-Provera CI use if jaundice or acute or chronic disturbances of liver function develop. Do not resume use until markers of liver function return to normal and Depo-Provera CI causation has been excluded.

5.8 Convulsions
There have been a few reported cases of convulsions in patients who were treated with Depo-Provera CI. Association with drug use or pre-existing conditions is not clear.

5.9 Depression
Monitor patients who have a history of depression and do not re-administer Depo-Provera CI if depression recurs.

5.10 Bleeding Irregularities
Most women using Depo-Provera CI experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include amenorrhea, irregular or unpredictable bleeding or spotting, prolonged spotting or bleeding, and heavy bleeding. Rule out the possibility of organic pathology if abnormal bleeding persists or is severe, and institute appropriate treatment.

As women continue using Depo-Provera CI, fewer experience irregular bleeding and more experience amenorrhea. In clinical studies of Depo-Provera CI, by month 12 amenorrhea was reported by 55% of women, and by month 24, amenorrhea was reported by 68% of women using Depo-Provera CI.

5.11 Weight Gain

Women tend to gain weight while on therapy with Depo-Provera CI. From an initial average body weight of 136 lb, women who completed 1-year of therapy with Depo-Provera CI 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.

5.12 Carbohydrate Metabolism

A decrease in glucose tolerance has been observed in some patients on Depo-Provera CI treatment. Monitor diabetic patients carefully while receiving Depo-Provera CI.

5.13 Lactation

Detectable amounts of drug have been identified in the milk of mothers receiving Depo-Provera CI. In nursing mothers treated with Depo-Provera CI, 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.

5.14 Fluid Retention

Because progestational drugs including Depo-Provera CI may cause some degree of fluid retention, monitor patients with conditions that might be influenced by this condition, such as epilepsy, migraine, asthma, and cardiac or renal dysfunction.

5.15 Return of Fertility

Return to ovulation and fertility is likely to be delayed after stopping Depo-Provera CI. In a large US study of women who discontinued use of Depo-Provera CI to become pregnant, data are available for 61% of them. Of the 188 women who discontinued the study to become pregnant, 114 became pregnant. 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 CI to become pregnant and who were lost to follow-up or changed their mind.

5.16 Sexually Transmitted Diseases

Patients should be counseled that Depo-Provera CI does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

5.17 Pregnancy

Although Depo-Provera CI should not be used during pregnancy, there appears to be little or no increased risk of birth defects in women who have inadvertently been exposed to medroxyprogesterone acetate injections in early pregnancy.

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.

5.18 Monitoring

A woman who is taking hormonal contraceptive should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.19 Interference with Laboratory Tests

The use of Depo-Provera CI may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins *[*see *Drug Interactions (7.2)]*.

6 ADVERSE REACTIONS

The following important adverse reactions observed with the use of Depo-Provera CI are discussed in greater detail in the *Warnings and Precautions* section (*5*):

- Loss of Bone Mineral Density *[*see *Warnings and Precautions (5.1)]*.
- Thromboembolic disease *[*see *Warnings and Precautions (5.2)]*.
- Breast Cancer *[*see *Warnings and Precautions (5.3)]*.
- Anaphylaxis and Anaphylactoid Reactions *[*see *Warnings and Precautions (5.5)]*.
- Potential Injection site reactions (including injection site necrosis and atrophy, which have been reported) *[*see *Warnings and Precautions (5.6)]*.
- Bleeding Irregularities *[*see *Warnings and Precautions (5.10)]*.
- Weight Gain *[*see *Warnings and Precautions (5.11)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the two clinical trials with Depo-Provera CI, 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 CI. The population studied ranges in age from 15 to 51 years, of which 46% were White, 50% Non-White, and 4.9% Unknown race. The patients received 150 mg Depo-Provera CI every 3 months (90 days). The median study duration was 13 months with a range of 1-84 months. Fifty eight percent of patients remained in the study after 13 months and 34% after 24 months.

Table 1 Adverse Reactions that were Reported by more than 5% of Subjects

Body System*	Adverse Reactions (Incidence (%))
Body as a Whole	Headache (16.5%) Abdominal pain/discomfort (11.2%)
Metabolic/Nutritional	Increased weight >10 lbs at 24 months (37.7%)
Nervous	Nervousness (10.8%) Dizziness (5.6%) Libido decreased (5.5%)
Urogenital	Menstrual irregularities: bleeding (57.3% at 12 months, 32.1% at 24 months) amenorrhea (55% at 12 months, 68% at 24 months)

* Body System represented from COSTART medical dictionary.

Table 2 Adverse Reactions that were Reported by between 1% and 5% of Subjects

Body System*	Adverse Reactions (Incidence (%))
Body as a Whole	Asthenia/fatigue (4.2%) Backache (2.2%) Dysmenorrhea (1.7%) Hot flashes (1.0%)
Digestive	Nausea (3.3%) Bloating (2.3%)
Metabolic/Nutritional	Edema (2.2%)
Musculoskeletal	Leg cramps (3.7%) Arthralgia (1.0%)
Nervous	Depression (1.5%) Insomnia (1.0%)
Skin and Appendages	Acne (1.2%) No hair growth/alopecia (1.1%) Rash (1.1%)
Urogenital	Leukorrhea (2.9%) Breast pain (2.8%) Vaginitis (1.2%)

* Body System represented from COSTART medical dictionary.

Adverse reactions leading to study discontinuation in ≥2% of subjects:
Bleeding (8.2%), amenorrhea (2.1%), weight gain (2.0%).

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Depo-Provera CI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been cases of osteoporosis including osteoporotic fractures reported post-marketing in patients taking Depo-Provera CI.

Table 3 Adverse Reactions Reported During Post-marketing Experience

Body System*	Adverse Reactions
Body as a Whole	Chest pain, Allergic reactions including angioedema, Fever, Injection site abscess†, Injection site infection†, Injection site nodule/lump, Injection site pain/tenderness, Injection site persistent atrophy/indentation/dimpling, Injection-site reaction, Lipodystrophy acquired, Chills, Axillary swelling
Cardiovascular	Syncope, Tachycardia, Thrombophlebitis, Deep vein thrombosis, Pulmonary embolus, Varicose veins
Digestive	Changes in appetite, Gastrointestinal disturbances, Jaundice, Excessive thirst, Rectal bleeding
Hematologic and Lymphatic	Anemia, Blood dyscrasia
Musculoskeletal	Osteoporosis
Neoplasms	Cervical cancer, Breast cancer
Nervous	Paralysis, Facial palsy, Paresthesia, Drowsiness
Respiratory	Dyspnea and asthma, Hoarseness
Skin and Appendages	Hirsutism, Excessive sweating and body odor, Dry skin, Scleroderma
Urogenital	Lack of return to fertility, Unexpected pregnancy, Prevention of lactation, Changes in breast size, Breast lumps or nipple bleeding, Galactorrhea, Melasma, Chloasma, Increased libido, Uterine hyperplasia, Genitourinary infections, Vaginal cysts, Dyspareunia

* Body System represented from COSTART medical dictionary.
† Injection site abscess and injection site infections have been reported; therefore strict aseptic injection technique should be followed when administering Depo-Provera CI in order to avoid injection site infections *[*see *Dosage and Administration (2.1)]*.

7 DRUG INTERACTIONS

7.1 Changes in Contraceptive Effectiveness Associated with Co-administration of Other Products

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates;
- bosentan;
- carbamazepine;
- felbamate;
- griseofulvin;
- oxcarbazepine;
- phenytoin;
- rifampin;

- St. John's Wort;
- topiramate.

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of progestin have been noted in some cases of co-administration of HIV protease inhibitors. Significant changes (increase or decrease) in the plasma levels of the progestin have been noted in some cases of co-administration with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 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 CI:

(a) Plasma and urinary steroid levels are decreased (e.g., 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.
T_3-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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Depo-Provera CI should not be administered during pregnancy *[*see *Contraindications (4)* and *Warnings and Precautions (5.17)]*.

8.2 Nursing Mothers

Detectable amounts of drug have been identified in the milk of mothers receiving Depo-Provera CI *[*see *Warnings and Precautions (5.13)]*.

8.3 Pediatric Use

Depo-Provera CI is not indicated before menarche. Use of Depo-Provera CI is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of Depo-Provera CI by younger women will reduce peak bone mass and increase the risk of osteoporotic fractures in later life. Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

8.4 Geriatric Use

This product has not been studied in post-menopausal women and is not indicated in this population.

8.5 Renal Impairment

The effect of renal impairment on Depo-Provera CI pharmacokinetics has not been studied.

8.6 Hepatic Impairment

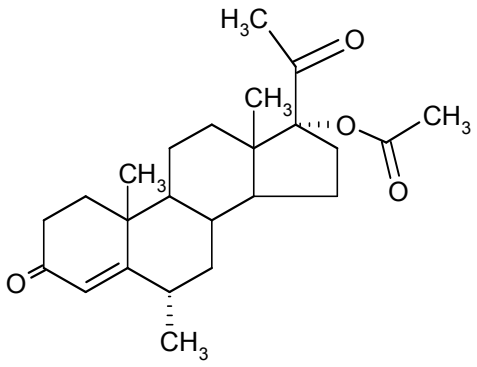
The effect of hepatic impairment on Depo-Provera CI pharmacokinetics has not been studied. Depo-Provera CI should not be used by women with significant liver disease and should be discontinued if jaundice or disturbances of liver function occur *[*see *Contraindications (4)* and *Warnings and Precautions (5.7)]*.

9 DESCRIPTION

Depo-Provera CI 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-, (6α-).

The structural formula is as follows:


H3C
O
CH3
O
CH3
CH3
O
O
CH3

Depo-Provera CI for intramuscular (IM) injection is available in vials, containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Depo-Provera CI (medroxyprogesterone acetate [MPA]), 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.

10.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Depo-Provera CI.

10.3 Pharmacokinetics

Absorption

Following a single 150 mg IM dose of Depo-Provera CI in eight women between the ages of 28 and 36 years old, 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.

Distribution

Plasma protein binding of MPA averages 86%. MPA binding occurs primarily to serum albumin. No binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolized in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

The concentrations of medroxyprogesterone acetate 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 CI is approximately 50 days. Most medroxyprogesterone acetate metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates.

Specific Populations

The effect of hepatic and/or renal impairment on the pharmacokinetics of Depo-Provera CI is unknown.

11 NON-CLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*[*see *Warnings and Precautions (5.3, 5.15,* and *5.17)]*.

12 CLINICAL STUDIES

12.1 Contraception

In five clinical studies using Depo-Provera CI, the 12-month failure rate for the group of women treated with Depo-Provera CI was zero (no pregnancies reported) to 0.7 by Life-Table method. The effectiveness of Depo-Provera CI is dependent on the patient returning every 3 months (13 weeks) for reinjection.

12.2 Bone Mineral Density (BMD) Changes in Adult Women

In a controlled, clinical study, adult women using Depo-Provera CI for up to 5 years showed spine and hip BMD mean decreases of 5%–6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4, and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of Depo-Provera CI (150 mg), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. Longer duration of treatment was associated with less complete recovery during this 2-year period following the last injection. Table 4 shows the change in BMD in women after 5 years of treatment with Depo-Provera CI and in women in a control group, as well as the extent of recovery of BMD for the subset of the women for whom 2-year post-treatment data were available.

Table 4 Mean Percent Change from Baseline in BMD in Adults by Skeletal Site and Cohort (5 Years of Treatment and 2 Years of Follow-Up)

Time in Study	Spine		Total Hip		Femoral Neck	
	Depo-Provera*	Control**	Depo-Provera*	Control**	Depo-Provera*	Control**
5 years	-5.38% n = 33	0.43% n = 105	-5.16% n = 21	0.19% n = 65	-6.12% n = 34	-0.27% n = 106
7 years	-3.13% n = 12	0.53% n = 60	-1.34% n = 7	0.94% n = 39	-5.38% n = 13	-0.11% n = 63

*The treatment group consisted of women who received Depo-Provera CI for 5 years and were then followed for 2 years post-use (total time in study of 7 years).

**The control group consisted of women who did not use hormonal contraception and were followed for 7 years.

12.3 Bone Mineral Density Changes in Adolescent Females (12-18 years of age)

The impact of Depo-Provera CI (150 mg) use for up to 240 weeks (4.6 years) was evaluated in an open-label non-randomized clinical study in 389 adolescent females (12-18 years). Use of Depo-Provera CI was associated with a significant decline from baseline in BMD.

Partway through the trial, drug administration was stopped (at 120 weeks). The mean number of injections per Depo-Provera CI user was 9.3. The decline in BMD at total hip and femoral neck was greater with longer duration of use (see Table 5). The mean decrease in BMD at 240 weeks was more pronounced at total hip (-6.4%) and femoral neck (-5.4%) compared to lumbar spine (-2.1%).

In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynecologic age, race, BMD and other factors that influence the rate of acquisition of bone mineral density.

Table 5 Mean Percent Change from Baseline in BMD in Adolescents Receiving ≥4 Injections per 60-week Period, by Skeletal Site and Cohort

Duration of Treatment	Depo-Provera CI (150 mg IM)		Unmatched, Untreated Cohort	
	N	Mean % Change	N	Mean % Change
Total Hip BMD				
Week 60 (1.2 years)	113	-2.75	166	1.22
Week 120 (2.3 years)	73	-5.40	109	2.19
Week 240 (4.6 years)	28	-6.40	84	1.71
Femoral Neck BMD				
Week 60	113	-2.96	166	1.75
Week 120	73	-5.30	108	2.83
Week 240	28	-5.40	84	1.94
Lumbar Spine BMD				
Week 60	114	-2.47	16	3.39
Week 120	73	-2.74	7	5.28
Week 240	27	-2.11	10	6.40
			9	
			84	

BMD recovery post-treatment in adolescent women

Longer duration of treatment and smoking were associated with less recovery of BMD following the last injection of Depo-Provera CI. Table 6 shows the extent of recovery of BMD up to 60 months post-treatment for adolescent women who received Depo-Provera CI for two years or less compared to more than two years. Post-treatment follow-up showed that, in women treated for more than two years, only lumbar spine BMD recovered to baseline levels after treatment was discontinued. Subjects treated with Depo-Provera for more than two years did not recover to their baseline BMD level at femoral neck and total hip even up to 60 months post-treatment. Adolescent women in the untreated cohort gained BMD throughout the trial period (data not shown).

Table 6 Extent of BMD Recovery (Months Post-treatment) in Adolescents by Years of Depo-Provera CI Use (2 Years or Less vs. More than 2 Years)

Duration of Treatment	2 years or less		More than 2 years	
	N	Mean % Change from baseline	N	Mean % Change from baseline
Total Hip BMD				
End of Treatment	49	-1.5%	49	-6.2%
12 M post-treatment	33	-1.4%	24	-4.6%
24 M post-treatment	18	0.3%	17	-3.6%
36 M post-treatment	12	2.1%	11	-4.6%
48 M post-treatment	10	1.3%	9	-2.5%
60 M post-treatment	3	0.2%	2	-1.0%
Femoral Neck BMD				
End of Treatment	49	-1.6%	49	-5.8%
12 M post-treatment	33	-1.4%	24	-4.3%
24 M post-treatment	18	0.5%	17	-3.8%
36 M post-treatment	12	1.2%	11	-3.8%
48 M post-treatment	10	2.0%	9	-1.7%
60 M post-treatment	3	1.0%	2	-1.9%
Lumbar Spine BMD				
End of Treatment	49	-0.9%	49	-3.5%
12 M post-treatment	33	0.4%	23	-1.1%
24 M post-treatment	18	2.6%	17	1.9%
36 M post-treatment	12	2.4%	11	0.6%
48 M post-treatment	10	6.5%	9	3.5%
60 M post-treatment	3	6.2%	2	5.7%

12.4 Relationship of fracture incidence to use of DMPA 150 mg IM or non-use by women of reproductive age

A retrospective cohort study to assess the association between DMPA injection and the incidence of bone fractures was conducted in 312,395 female contraceptive users in the UK. The incidence rates of fracture were compared between DMPA users and contraceptive users who had no recorded use of DMPA. The Incident Rate Ratio (IRR) for any fracture during the follow-up period (mean = 5.5 years) was 1.41 (95% CI 1.35, 1.47). It is not known if this is due to DMPA use or to other related lifestyle factors that have a bearing on fracture rate.

In the study, when cumulative exposure to DMPA was calculated, the fracture rate in users who received fewer than 8 injections was higher than that in women who received 8 or more injections. However, it is not clear that cumulative exposure, which may include periods of intermittent use separated by periods of non-use, is a useful measure of risk, as compared to exposure measures based on continuous use.

There were very few osteoporotic fractures (fracture sites known to be related to low BMD) in the study overall, and the incidence of osteoporotic fractures was not found to be higher in DMPA users compared to non-users. Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life.

13 HOW SUPPLIED/STORAGE AND HANDLING

Depo-Provera CI is supplied in the following strengths and package configurations:

Package Configuration	Strength
Depo-Provera CI (medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL)	
1 mL vial	150 mg/mL

Vials MUST be stored upright at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP].

14 PATIENT COUNSELING INFORMATION

- Advise patients 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 CI continues, without other therapy being required.
- Counsel patients about the possible increased risk of breast cancer in women who use Depo-Provera CI.
- Counsel patients that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with use of Depo-Provera CI.
- Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with Depo-Provera CI.

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