DEPO-PROVERA 150 mg/mL
(Medroxyprogesterone acetate)
Suspension for injection

WARNING: LOSS OF BONE MINERAL DENSITY

Women who use Depo-Provera Suspension for 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 Suspension for 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 Suspension for 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 (8.1)*].

1. NAME OF THE MEDICINAL PRODUCT

DEPO-PROVERA 150 mg/mL Suspension for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of DEPO-PROVERA 150mg/mL contains: Medroxyprogesterone acetate 150 mg.

Excipient(s)
For a full list of excipients, see section 13.1

3. ROUTE OF ADMINISTRATION
Intramuscular

4. PHARMACEUTICAL FORM
Suspension for injection

5. INDICATIONS AND USAGE

DEPO-PROVERA 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 long-term [*see Warnings and Precautions (8.1)*].

6. DOSAGE AND ADMINISTRATION

6.1 Prevention of Pregnancy

Both the 1 mL vial and the 1 mL prefilled syringe of Depo-Provera 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 every 3 months (13 weeks) administered by deep intramuscular (IM) injection using strict aseptic technique in the gluteus 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 should not be used as a long-term birth control method (e.g., longer than 2 years) unless other birth control methods are considered inadequate. Dosage does not need to be adjusted for body weight.

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 breastfeeding; and if exclusively breastfeeding, 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 depends on adherence to the dosage schedule of administration.

6.2 Switching from Other Methods of Contraception

When switching from other contraceptive methods, Depo-Provera 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 Suspension for Injection on the day after the last active tablet or at the latest, on the day following the final inactive tablet).

7. CONTRAINDICATIONS

The use of Depo-Provera 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 (8.2)]*
- Known or suspected malignancy of breast *[see Warnings and Precautions (8.3)]*
- Known hypersensitivity to DEPO-PROVERA (medroxyprogesterone acetate) or any of its other ingredients. *[see Warnings and Precautions (8.5)]*
- Significant liver disease *[see Warnings and Precautions (8.7)]*
- Undiagnosed vaginal bleeding *[see Warnings and Precautions (8.10)]*

8. WARNINGS AND PRECAUTIONS

8.1 Loss of Bone Mineral Density

Use of Depo-Provera 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 by younger women would reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

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

Depo-Provera should not be used as a long-term birth control method (e.g., longer than 2 years) unless other birth control methods might be considered inadequate. BMD should be evaluated when a woman needs to continue to use Depo-Provera 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 in women with osteoporosis risk factors. Depo-Provera 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, all patients should have adequate calcium and Vitamin D intake.

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

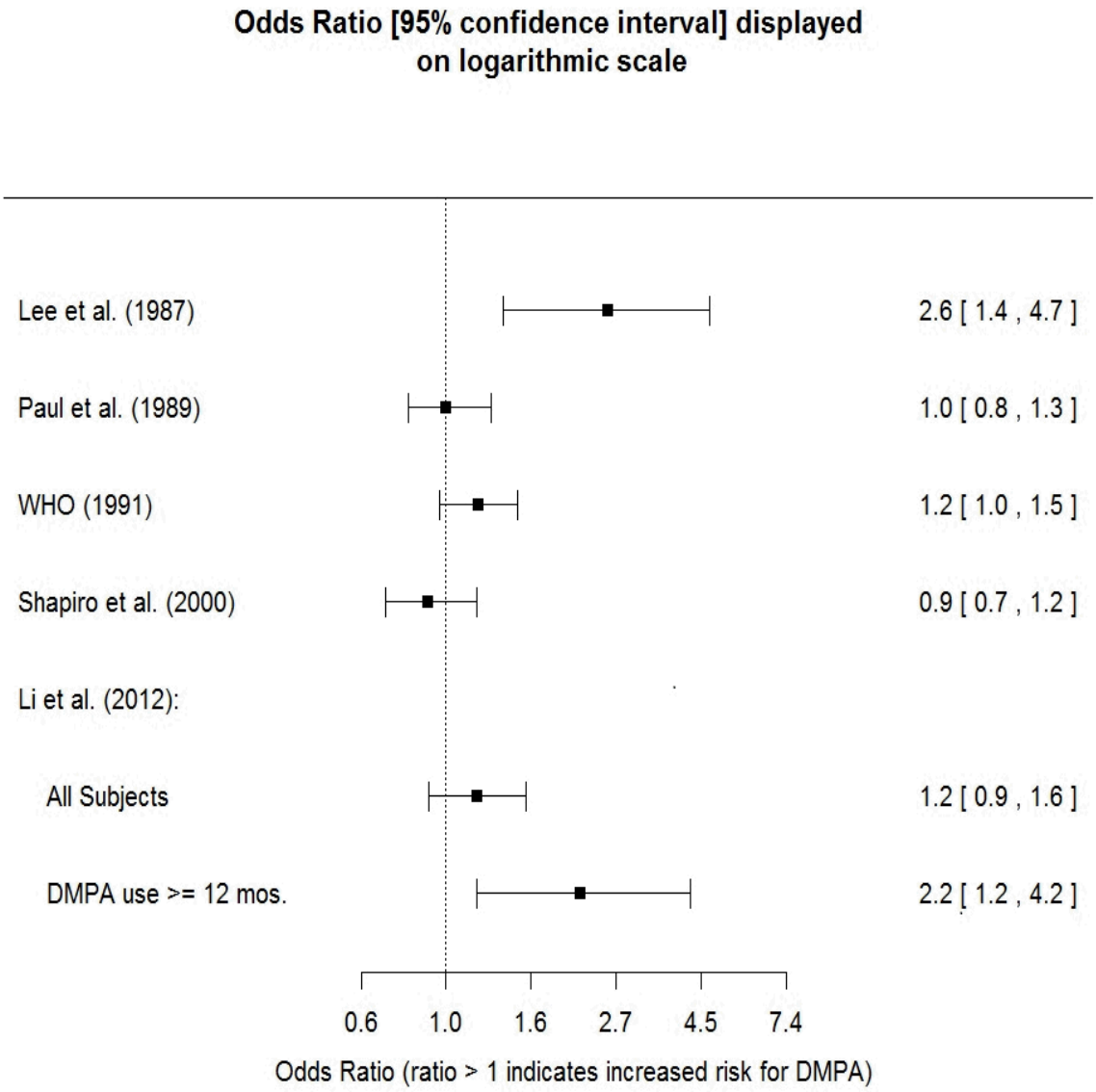
Do not re-administer Depo-Provera until evaluation in cases of a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. Do not re-administer if examination reveals papilledema or retinal vascular lesions.

8.3 Cancer Risks

Breast Cancer
Women who have or have had a history of breast cancer should not use hormonal contraceptives, including Depo-Provera, because breast cancer may be hormonally sensitive *[see Contraindications (7)]*. 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 summarize 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 finding 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 from about 72 to about 144 cases per 100,000 women.

Cervical Cancer
A statistically nonsignificant increase in RR estimates of invasive squamous-cell cervical cancer has been associated with the use of Depo-Provera 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 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 found no overall increased risk of ovarian or liver cancer.

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

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

8.6 Injection Site Reactions
Injection site reactions have been reported with use of Depo-Provera *[see Adverse Reactions (9.2)]*. Persistent injection site reactions may occur after administration of Depo-Provera due to inadvertent subcutaneous administration or release of the drug into the subcutaneous space while removing the needle *[see Dosage and Administration (6.1)]*.

8.7 Liver Function
Discontinue Depo-Provera 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 causation has been excluded.

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

8.9 Depression
Monitor patients who have a history of depression and do not readminister Depo-Provera if depression recurs.

8.10 Bleeding Irregularities
Most women using Depo-Provera 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, fewer experience irregular bleeding and more experience amenorrhea. In clinical studies of Depo-Provera, by month 12 amenorrhea was reported by 55% of women, and by month 24, amenorrhea was reported by 68% of women using Depo-Provera.

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

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

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

8.14 Fluid Retention
Because progestational drugs including Depo-Provera 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.

8.15 Return of Fertility
Return to ovulation and fertility is likely to be delayed after stopping Depo-Provera Suspension for Injection. In a large US study of women who discontinued use of Depo-Provera 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 to become pregnant and who were lost to follow-up or changed their mind.

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

8.17 Pregnancy
Although Depo-Provera 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.

8.18 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.

8.19 Interference with Laboratory Tests
The use of Depo-Provera may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins *[see Drug Interactions (10.2)]*.

As it contains methylparaben as an excipient, this medication may cause hives. In general it can produce delayed reactions such as contact dermatitis. On rare occasions it can cause immediate reactions such as hives and bronchospasms.

9. UNDESIRABLE EFFECTS

The following important adverse reactions observed with the use of Depo-Provera are discussed in greater detail in the *Warnings and Precautions* section (8):

- Loss of bone mineral density (BMD) *[see Warnings and Precautions (8.1)]*
- Thromboembolic disease *[see Warnings and Precautions (8.2)]*
- Breast cancer *[see Warnings and Precautions (8.3)]*
- Anaphylaxis and anaphylactoid reactions *[see Warnings and Precautions (8.5)]*
- Bleeding irregularities*[see Warnings and Precautions (8.9)]*
- Weight gain *[see Warnings and Precautions (8.10)]*

9.1 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, over 3900 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. 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 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 (5 Kg Approx.) 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 patients: bleeding (8.2%), amenorrhea (2.1%), weight gain (2.0%).

9.2 Post-marketing Experience
The following adverse reactions have been identified during post approval use of Depo-Provera.

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.

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 in order to avoid injection site infections *[see Dosage and Administration (6.1)]*.

10. DRUG INTERACTIONS

10.1 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 an 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 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.

10.2 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:

(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. 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.

11. USE IN SPECIFIC POPULATIONS

11.1 Pregnancy
Depo-Provera should not be administered during pregnancy. [See *Contraindications (7) and Warnings and Precautions (8.16)]*

11.2 Nursing Mothers
Detectable amounts of drug have been identified in the milk of mothers receiving Depo-Provera *[*see *Warnings and Precautions (8.12)]*

11.3 Pediatric Use
Depo-Provera is not indicated before menarche. Use of Depo-Provera 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 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 postmenarchal adolescents and adult women.

11.4 Geriatric Use
This product has not been studied in postmenopausal women and is not indicated in this population.

11.5 Renal Impairment
The effect of renal impairment on Depo-Provera pharmacokinetics has not been studied.

11.6 Hepatic Impairment

The effect of hepatic impairment on Depo-Provera pharmacokinetics has not been studied. Depo-Provera should not be used by women with significant liver disease and should be discontinued if jaundice or disturbances of liver function occur *[*see *Contraindications (7)* and *Warnings and Precautions (8.6)]*.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Depo-Provera (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.

12.2 Pharmacodynamics
No specific pharmacodynamic studies were conducted with Depo-Provera suspension for injection.

12.3 Pharmacokinetics

Absorption
Following a single 150 mg IM dose of Depo-Provera 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
Medroxyprogesterone acetate 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 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 is unknown.

13. PHARMACEUTICAL PARTICULARS

13.1 List of Excipients
Polysorbate 80, Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Macrogol (Polyethylene glycol) 3350, Sodium chloride, Hydrochloric acid, Sodium hydroxide and Water for injection.

13.2 Incompatibilities
None known

13.3 Shelf Life
Do not use the product after the expiry date indicated on the package

13.4 Special Storage Precautions

See storage conditions indicated on the package

13.5 Special Precautions for Disposal and Other Handling
No special requirements

13.6 Effects on ability to drive and use machines
None known.

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