MEDROXYPROGESTERONE ACETATE

Injectable Suspension, USP

PRODUCT	DELIVERY SYSTEM	UNIT SIZE	UNITS / BOX	NDC#
Medroxyprogesterone Acetate Inj., USP [150 mg/mL]	Prefilled Syringe	150 mg / 1 mL	1	0548-5701-00
Medroxyprogesterone Acetate Inj., USP [150 mg/mL]	Single Dose Vial	150 mg / 1 mL	1	0548-5400-00
Medroxyprogesterone Acetate Inj., USP [150 mg/mL]	Single Dose Vial	150 mg / 1 mL	25	0548-5400-25

	WHOLESALER ITEM NUMBERS			
NDC#	AMERISOURCE BERGEN	CARDINAL	MCKESSON	MORRIS & DICKSON
0548-5701-00	10184252	5417860	3751005	209791
0548-5400-00	10184250	5417845	3751013	209692
0548-5400-25	10184254	5417852	3757820	209783

For more information,
PLEASE CALL 1-800-423-4136

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See over for full prescribing information

Rx Only
01/18
01-506-01

MEDROXYPROGESTERONE ACETATE
INJECTABLE SUSPENSION

Full Prescribing Information

WARNING: LOSS OF BONE MINERAL DENSITY

Women who use Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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.

Medroxyprogesterone acetate 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

Medroxyprogesterone acetate 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 Medroxyprogesterone acetate long-term *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Pregnancy

Both the 1 mL vial and the 1 mL prefilled syringe of Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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.

Medroxyprogesterone acetate 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 (14.1)]*.

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 Medroxyprogesterone acetate depends on adherence to the dosage schedule of administration.

2.2 Switching from other Methods of Contraception

When switching from other contraceptive methods, Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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

Prefilled syringes are available packaged with a 22-gauge x 1 1/2 inch Needle Pro® EDGE™ Safety Device.

4 CONTRAINDICATIONS

The use of Medroxyprogesterone acetate 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 Medroxyprogesterone acetate or any of its other ingredients *[see Warnings and Precautions (5.5)]*.
- Significant liver disease *[see Warnings and Precautions (5.6)]*.
- Undiagnosed vaginal bleeding *[see Warnings and Precautions (5.9)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Loss of Bone Mineral Density

Use of Medroxyprogesterone acetate 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 Medroxyprogesterone acetate by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

After discontinuing Medroxyprogesterone acetate 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 (14.3)]*. 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 (14.2).]*

Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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 Medroxyprogesterone acetate in women with osteoporosis risk factors. Medroxyprogesterone acetate 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 Medroxyprogesterone acetate, 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 Medroxyprogesterone acetate (150 mg). However, Medroxyprogesterone acetate has not been causally associated with the induction of thrombotic or thromboembolic disorders. Any patient who develops thrombosis while undergoing therapy with Medroxyprogesterone acetate should discontinue treatment unless she has no other acceptable options for birth control.

Do not re-administer Medroxyprogesterone acetate 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.

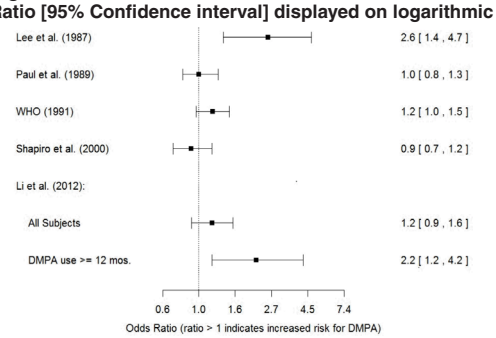
5.3 Cancer Risks

Breast Cancer

Women who have or have had a history of breast cancer should not use hormonal contraceptives, including Medroxyprogesterone acetate, 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[1, 2, 3, 4, 5] assessing the association between depomedroxyprogesterone 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[1] 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[4].

Figure 1 Risk estimates for breast cancer in DMPA users
Odds Ratio [95% Confidence interval] displayed on logarithmic scale



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 years6, a doubling of risk would increase the incidence of breast cancer in women who use Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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

Medroxyprogesterone acetate. Institute emergency medical treatment if an anaphylactic reaction occurs.

5.6 Injection Site Reactions

Injection site reactions have been reported with use of Medroxyprogesterone acetate *[see Adverse Reactions (6.2)]*. Persistent injection site reactions may occur after administration of Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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 Medroxyprogesterone acetate causation has been excluded.

5.8 Convulsions

There have been a few reported cases of convulsions in patients who were treated with Medroxyprogesterone acetate. 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 readminister Medroxyprogesterone acetate if depression recurs.

5.10 Bleeding Irregularities

Most women using Medroxyprogesterone acetate 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 Medroxyprogesterone acetate, fewer experience irregular bleeding and more experience amenorrhea. In clinical studies of Medroxyprogesterone acetate, by month 12 amenorrhea was reported by 55% of women, and by month 24, amenorrhea was reported by 68% of women using Medroxyprogesterone acetate.

5.11 Weight Gain

Women tend to gain weight while on therapy with Medroxyprogesterone acetate. From an initial average body weight of 136 lb, women who completed 1 year of therapy with Medroxyprogesterone acetate 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 Medroxyprogesterone acetate treatment. Monitor diabetic patients carefully while receiving Medroxyprogesterone acetate.

5.13 Lactation

Detectable amounts of drug have been identified in the milk of mothers receiving Medroxyprogesterone acetate. In nursing mothers treated with Medroxyprogesterone acetate, 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 Medroxyprogesterone acetate 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 Medroxyprogesterone acetate. In a large US study of women who discontinued use of Medroxyprogesterone acetate 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 Medroxyprogesterone acetate to become pregnant and who were lost to follow-up or changed their mind.

5.16 Sexually Transmitted Diseases

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

5.17 Pregnancy

Although Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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 Medroxyprogesterone acetate 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)]*
- 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 Medroxyprogesterone acetate, 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 Medroxyprogesterone acetate. 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 Medroxyprogesterone acetate 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 (1%)]
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.