

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-553

APPROVED LABELING

PATIENT LABELING

Package Insert

Rx only

GensiaSicor
PHARMACEUTICALS

Medroxyprogesterone
Acetate Injectable Suspension, USP
Contraceptive Injection

Y36-000-L4A

Package Insert

Rx only

GensiaSicor
PHARMACEUTICALS

Medroxyprogesterone
Acetate Injectable Suspension, USP
Contraceptive Injection

APPROVED

JUL 28 2004

This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PATIENT LABELING

Introduction

Every woman who considers using medroxyprogesterone acetate injectable suspension, USP needs to understand the benefits and risks of this form of birth control and to discuss them with her health-care provider. This leaflet is intended to give you much of the information you will need in order to decide if medroxyprogesterone acetate injectable suspension is the right choice for you. Your health-care provider will help you to compare medroxyprogesterone acetate injectable suspension with other contraceptive methods and will answer any questions you have after you have read this information.

Medroxyprogesterone acetate injectable suspension is given as an intramuscular injection (a shot) in the buttock or upper arm once every 3 months (13 weeks). Promptly at the end of the 3-month interval, you will need to return to your health-care provider for your next injection in order to continue your contraceptive protection.

Medroxyprogesterone acetate injectable suspension contains medroxyprogesterone acetate, a chemical similar to (but not the same as) the natural hormone progesterone that is produced by your ovaries during the second half of your menstrual cycle. Medroxyprogesterone acetate injectable suspension acts by preventing your egg cells from ripening. If an egg is not released from the ovaries during your menstrual cycle, it cannot become fertilized by sperm and result in pregnancy. Medroxyprogesterone acetate injectable suspension also causes changes in the lining of your uterus that make it less likely for pregnancy to occur.

Effectiveness of Medroxyprogesterone Acetate Injectable Suspension

To ensure that medroxyprogesterone acetate injectable suspension 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 **Administration of Medroxyprogesterone Acetate Injectable Suspension**). The efficacy of medroxyprogesterone acetate injectable suspension depends on adherence to the recommended dosage schedule.

Medroxyprogesterone acetate injectable suspension is over 99% effective, making it one of the most reliable methods of birth control available. This means that the average annual pregnancy rate is less than one for every 100 women using this method.

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 **Administration of Medroxyprogesterone Acetate Injectable Suspension**). The efficacy of medroxyprogesterone acetate injectable suspension depends on adherence to the recommended dosage schedule.

Medroxyprogesterone acetate injectable suspension is over 99% effective, making it one of the most reliable methods of birth control available. This means that the average annual pregnancy rate is less than one for every 100 women who use medroxyprogesterone acetate injectable suspension. The effectiveness of most contraceptive methods depends, in part, on how reliably each woman uses the method. The effectiveness of medroxyprogesterone acetate injectable suspension depends only on the patient returning every 3 months (13 weeks) for her next injection.

The following table shows the percent of women who become pregnant while using different kinds of contraceptive methods. It gives both the lowest expected rate of pregnancy (the rate expected in women who use each method exactly as it should be used) and the typical rate of pregnancy (which includes women who became pregnant because they forgot to use their birth control or because they did not follow the directions exactly).

Percent of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use

Method	Lowest Expected	Typical
Medroxyprogesterone	0.3	0.3
Implants (Norplant)	0.2*	0.2*
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15
Oral contraceptives (pill)	—	3
Combined	0.1	—
Progestogen only	0.5	—
IUD	—	3
Progestasert	2	—
Copper T 380A	0.8	—
Condom (without spermicide)	2	12
Diaphragm (with spermicide)	6	18
Cervical cap	6	18
Withdrawal	4	18
Periodic abstinence	1-9	20
Spermicide alone	3	21
Vaginal sponge	—	—
used before childbirth	6	18
used after childbirth	9	28
No method	85	85

Source: Trussell et al; *Obstet Gynecol* 1990;76:558-567.

* From Norplant® package insert.

Who Should Not Use Medroxyprogesterone Acetate Suspension

Certain women should not use medroxyprogesterone acetate injectable suspension. You should not use medroxyprogesterone acetate injectable suspension if you have any of the following conditions:

- if you think you might be pregnant
- if you have any vaginal bleeding without a known reason
- if you have had cancer of the breast
- if you have had a stroke
- if you have or have had blood clots (phlebitis) in your legs
- if you have problems with your liver or liver disease
- if you are allergic to medroxyprogesterone acetate injectable suspension (medroxyprogesterone acetate or any of its other ingredients)

Other Things to Consider Before Choosing Medroxyprogesterone Acetate Injectable Suspension

Before your doctor prescribes medroxyprogesterone acetate injectable

- 3
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 - if you have had a stroke
 - if you have or have had blood clots (phlebitis) in your legs
 - if you have problems with your liver or liver disease
 - if you are allergic to medroxyprogesterone acetate injectable suspension (medroxyprogesterone acetate or any of its other ingredients)

Other Things to Consider Before Choosing Medroxyprogesterone Acetate Injectable Suspension

Before your doctor prescribes medroxyprogesterone acetate injectable suspension, you will have a physical examination. It is important to tell your doctor or health-care provider if you have any of the following:

- a family history of cancer of the breast
- an abnormal mammogram (breast X-ray), fibrocystic breast disease, breast nodules or lumps, or bleeding from your nipples
- kidney disease
- irregular or scanty menstrual periods
- high blood pressure
- migraine headaches
- asthma
- epilepsy (convulsions or seizures)
- diabetes or a family history of diabetes
- a history of depression
- if you are taking any prescription or over-the-counter medications

This product is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

Return of Fertility

Because medroxyprogesterone acetate injectable suspension is a long-acting birth control method, it takes some time after your last injection for its effect to wear off. Based on the results from a large study done in the United States, of those women who stop using medroxyprogesterone acetate injectable suspension in order to become pregnant, about half of those who become pregnant do so in about 10 months after their last injection; about two-thirds of those who become pregnant do so in about 12 months, about 83% of those who become pregnant do so in about 15 months, and about 93% of those who become pregnant do so in about 18 months after their last injection. The length of time you use medroxyprogesterone acetate injectable suspension has no effect on how long it takes you to become pregnant after you stop using it.

Risks of Using Medroxyprogesterone Acetate Injectable Suspension

1. Irregular Menstrual Bleeding

The side effect reported most frequently by women who use medroxyprogesterone acetate injectable suspension for contraception is a change in their normal menstrual cycle. During the first year of using medroxyprogesterone acetate injectable suspension you might have one or more of the following changes:

- irregular or unpredictable bleeding or spotting,
- an increase or decrease in menstrual bleeding, or
- no bleeding at all.

Unusually heavy or continuous bleeding, however, is not a usual effect of medroxyprogesterone acetate injectable suspension and if this happens you should see your health-care provider right away.

With continued use of medroxyprogesterone acetate injectable suspension, bleeding usually decreases and many women stop having periods completely. In clinical studies of medroxyprogesterone acetate injectable suspension, 55% of the women studied reported

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With continued use of medroxyprogesterone acetate injectable suspension, bleeding usually decreases and many women stop having periods completely. In clinical studies of medroxyprogesterone acetate injectable suspension, 55% of the women studied reported no menstrual bleeding (amenorrhea) after 1 year of use and 68% of the women studied reported no menstrual bleeding after 2 years of use.

The reason that your periods stop is because medroxyprogesterone acetate injectable suspension causes a resting state in your ovaries. When your ovaries do not release an egg monthly, the regular monthly growth of the lining of your uterus does not occur and, therefore, the bleeding that comes with your normal menstruation does not take place. When you stop using medroxyprogesterone acetate injectable suspension your menstrual period will usually, in time, return to its normal cycle.

2. Bone Mineral Changes

Use of medroxyprogesterone acetate injectable suspension may be associated with a decrease in the amount of mineral stored in your bones. This could increase your risk of developing bone fractures. The rate of bone mineral loss is greatest in the early years of medroxyprogesterone acetate injectable suspension use but, after that, it begins to resemble the normal rate of age-related bone mineral loss.

3. Cancer

Studies of women who have used different forms of contraception found that women who used medroxyprogesterone acetate injectable suspension for contraception had no increased overall risk of developing cancer of the breast, ovary, uterus, cervix, or liver. However, women under 35 years of age whose first exposure to medroxyprogesterone acetate injectable suspension was within the previous 4 to 5 years may have a slightly increased risk of developing breast cancer similar to that seen with oral contraceptives. You should discuss this with your health-care provider.

4. Unexpected Pregnancy

Because medroxyprogesterone acetate injectable suspension is such an effective contraceptive method, the risk of unexpected pregnancy for women who get their shots regularly (every 3 months [13 weeks]) is very low. While there have been reports of an increased risk of low birth weight and neonatal infant death or other health problems in infants conceived close to the time of injection, such pregnancies are uncommon. If you think you may have become pregnant while using medroxyprogesterone acetate injectable suspension for contraception, see your health-care provider as soon as possible.

5. Allergic Reactions

Severe allergic reactions known as anaphylaxis and anaphylactoid reactions have also been reported in some women using medroxyprogesterone acetate injectable suspension.

6. Other Risks

Women who use hormone-based contraceptives may have an increased risk of blood clots or stroke. Also, if a contraceptive method fails, there is a possibility that the fertilized egg will begin to develop outside of the uterus (ectopic pregnancy). While these events are rare, you should tell your health-care provider if you have any of the **Warning Signals** listed in the next section.

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Warning Signals

If any of these problems occur following an injection of medroxyprogesterone acetate injectable suspension, call your health-care provider immediately:

- Sharp chest pain, coughing up of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Sudden severe headache or vomiting, dizziness or fainting, problems with your eyesight or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Severe pain or swelling in the calf (indicating a possible clot in the leg)
- Unusually heavy vaginal bleeding
- Severe pain or tenderness in the lower abdominal area
- Persistent pain, pus, or bleeding at the injection site

Side Effects of Medroxyprogesterone Acetate Injectable Suspension

1. Weight Gain

You may experience a weight gain while you are using medroxyprogesterone acetate injectable suspension. About two-thirds of the women who used medroxyprogesterone acetate injectable suspension in the clinical trials reported a weight gain of about 5 pounds during the first year of use. You may continue to gain weight after the first year. Women in one large study who used medroxyprogesterone acetate injectable suspension for 2 years gained an average total of 8.1 pounds over those 2 years, or approximately 4 pounds per year. Women who continued for 4 years gained an average total of 13.8 pounds over those 4 years, or approximately 3.5 pounds per year. Women who continued for 6 years gained an average total of 16.5 pounds over those 6 years, or approximately 2.75 pounds per year.

2. Other Side Effects

In a clinical study of over 3,900 women who used medroxyprogesterone acetate injectable suspension for up to 7 years, some women reported the following effects that may or may not have been related to their use of medroxyprogesterone acetate injectable suspension:

- irregular menstrual bleeding
- amenorrhea
- headache
- nervousness
- abdominal cramps
- dizziness
- weakness or fatigue
- decreased sexual desire
- leg cramps
- nausea
- vaginal discharge or irritation
- breast swelling and tenderness
- bloating
- swelling of the hands or feet
- backache
- depression
- insomnia
- acne
- pelvic pain
- no hair growth or excessive hair loss
- rash
- hot flashes
- joint pain

Other problems were reported by very few of the women in the clinical trials, but some of these could be serious. These include: convulsions, jaundice, urinary tract infections, allergic reactions, fainting, paralysis, osteoporosis, lack of

- acne
- pelvic pain
- no hair growth or excessive hair loss
- rash
- hot flashes
- joint pain

Other problems were reported by very few of the women in the clinical trials, but some of these could be serious. These include: convulsions, jaundice, urinary tract infections, allergic reactions, fainting, paralysis, osteoporosis, lack of return to fertility, deep vein thrombosis, pulmonary embolus, breast cancer, or cervical cancer. If these or any other problems occur during your use of medroxyprogesterone acetate injectable suspension, discuss them with your health-care provider.

General Precautions

1. Missed Periods

During the time you are using medroxyprogesterone acetate injectable suspension for contraception, you may skip a period, or your periods may stop completely. If you have been receiving your injection of medroxyprogesterone acetate injectable suspension regularly every 3 months (13 weeks), then you are probably not pregnant. However, if you think that you may be pregnant, see your health-care provider.

2. Laboratory Test Interactions

If you are scheduled for any laboratory tests, tell your health-care provider that you are using medroxyprogesterone acetate injectable suspension for contraception. Certain blood tests are affected by hormones such as medroxyprogesterone acetate injectable suspension.

3. Drug Interactions

Cytadren (aminoglutethimide) is an anticancer drug that may significantly decrease the effectiveness of medroxyprogesterone acetate injectable suspension if the two drugs are given during the same time.

4. Nursing Mothers

Although medroxyprogesterone acetate injectable suspension can be passed to the nursing infant in the breast milk, no harmful effects have been found in these children. Medroxyprogesterone acetate injectable suspension does not prevent the breasts from producing milk, so it can be used by nursing mothers. However, to minimize the amount of medroxyprogesterone acetate injectable suspension that is passed to the infant in the first weeks after birth, you should wait until 6 weeks after childbirth before you start using medroxyprogesterone acetate injectable suspension for contraception.

Administration of Medroxyprogesterone Acetate Injectable Suspension

The recommended dose of medroxyprogesterone acetate injectable suspension is 150 mg every 3 months (13 weeks) given in a single intramuscular injection in the buttock or upper arm. To ensure that you are not pregnant at the time of the first injection, it is essential that the injection be given **ONLY** during the first 5 days of a normal menstrual period. If used following the delivery of a child, the first injection of medroxyprogesterone acetate injectable suspension **MUST** be given within 5 days after childbirth if you are not breast-feeding, or if you are exclusively breast-feeding, the injection **MUST** be given 6 weeks after childbirth. If you wait longer than 3 months (13 weeks) between injections, or longer than 6 weeks after delivery, your health-care provider should determine that you are not pregnant before giving you your injection of medroxyprogesterone acetate injectable suspension.

PROFESSIONAL LABELING

Package Insert

R_x only

GenistaSicor[®]
PHARMACEUTICALS

Medroxyprogesterone
Acetate Injectable Suspension, USP
Contraceptive Injection

Y36-000-L3A

Package Insert

R_x only

GenistaSicor[®]
PHARMACEUTICALS

Medroxyprogesterone
Acetate Injectable Suspension, USP
Contraceptive Injection

APPROVED

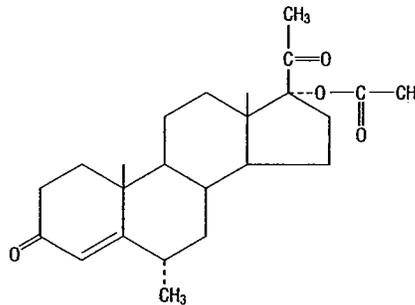
JUL 28 2004

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

DESCRIPTION

Medroxyprogesterone acetate injectable suspension, a 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

Medroxyprogesterone acetate injectable suspension, USP for intramuscular (IM) injection is available in vials 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

Medroxyprogesterone acetate injectable suspension, 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 medroxyprogesterone acetate injectable suspension, 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 medroxyprogesterone

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.

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Women with lower body weights conceive sooner than women with higher body weights after discontinuing medroxyprogesterone acetate injectable suspension.

The effect of hepatic and/or renal disease on the pharmacokinetics of medroxyprogesterone acetate injectable suspension is unknown.

INDICATIONS AND USAGE

Medroxyprogesterone acetate injectable suspension is indicated only for the prevention of pregnancy. To ensure that medroxyprogesterone acetate injectable suspension 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. The efficacy of medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension, the 12-month failure rate for the group of women treated with medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension, the efficacy of these contraceptive measures depends in part on the reliability of use. The effectiveness of medroxyprogesterone acetate injectable suspension 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 Medroxyprogesterone acetate injectable suspension	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		3
Combined	0.1	
Progestogen only	0.5	
IUD		3
Progestasert	2	
Copper T 380A	0.8	
Condom	2	12
Diaphragm	6	18
Cap	6	18
Spermicides	3	21
Sponge		
Parous women	9	28
Nulliparous women	6	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.

Source: Trussell et al.¹

* 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 medroxyprogesterone acetate injectable suspension (medroxyprogesterone acetate or any of its other ingredients).

WARNINGS

1. Bleeding Irregularities

Most women using medroxyprogesterone acetate injectable suspension 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.

As women continue using medroxyprogesterone acetate injectable suspension, 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 medroxyprogesterone acetate injectable suspension².

2. Bone Mineral Density Changes

Use of medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension found slight or no increased overall risk of breast cancer³ and no overall increased risk of ovarian⁴, liver⁵, 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 medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension. The RR of breast cancer for women of all ages who had initiated use of medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension 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 Institute⁸ 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 medroxyprogesterone acetate injectable suspension 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

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A statistically insignificant increase in RR estimates or invasive squamous-cell cervical cancer has been associated with the use of medroxyprogesterone acetate injectable suspension 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 injectable suspension 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 medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension may be at an increased risk of low birth weight, which, in turn, is associated with an increased 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 medroxyprogesterone acetate injectable suspension, 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 medroxyprogesterone acetate injectable suspension, 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 intrauterine 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 medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension who become pregnant or complain of severe abdominal pain.

8. Lactation

Detectable amounts of drug have been identified in the milk of mothers receiving medroxyprogesterone acetate injectable suspension. In nursing mothers treated with medroxyprogesterone acetate injectable suspension, 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 medroxyprogesterone acetate injectable suspension. 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 medroxyprogesterone acetate injectable suspension. The physical examination, however, may be deferred until after initiation of medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension. From an initial average body weight of 136 lb, women who completed 1 year of therapy with medroxyprogesterone acetate injectable suspension 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.

4. Return of Fertility

Medroxyprogesterone acetate injectable suspension has a prolonged contraceptive effect. In a large US study of women who discontinued use of medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension. 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 medroxyprogesterone acetate injectable suspension 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

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 medroxyprogesterone acetate injectable suspension may significantly depress the serum concentrations of medroxyprogesterone acetate.¹² Users of medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension:

- (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 of medroxyprogesterone acetate injectable suspension 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 medroxyprogesterone acetate injectable suspension, as compared with other forms 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 medroxyprogesterone acetate injectable suspension continues, without other therapy being required.

ADVERSE REACTIONS

In the largest clinical trial with medroxyprogesterone acetate injectable suspension, 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 injectable suspension.

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

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

Adverse reactions reported by 1% to 5% of subjects using medroxyprogesterone acetate injectable suspension were:

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Weight changes
Headache
Nervousness
Abdominal pain or discomfort
Dizziness
Asthenia (weakness or fatigue)

Adverse reactions reported by 1% to 5% of subjects using medroxyprogesterone acetate injectable suspension were:

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

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 medroxyprogesterone acetate injectable suspension.

DOSAGE AND ADMINISTRATION

The 1 mL vial of medroxyprogesterone acetate injectable suspension 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 injectable suspension 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 medroxyprogesterone acetate injectable suspension depends on adherence to the dosage schedule of administration.

HOW SUPPLIED

Medroxyprogesterone Acetate Injectable Suspension, USP is available as:

NDC Number	Concentration	Package Size
0703-6801-01	150 mg/mL	1 mL vials packaged individually
0703-6801-04	150 mg/mL	1 mL vials packaged 25 vials per shelf carton

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature.]

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3. WHO Collaborative Study of Neolasia and Steroid

0703-6801-04 150 mg/mL

packaged intramuscularly
1 mL vials
packaged 25 vials per
shelf carton

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature.]

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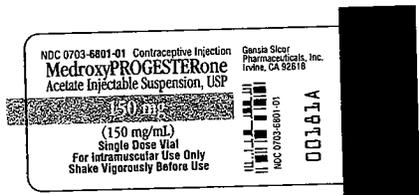
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Gensia Sicor Pharmaceuticals, Inc.
Medroxyprogesterone Acetate Injectable Suspension, USP
ANDA 76-553
Response to Agency Facsimile Dated March 24, 2003

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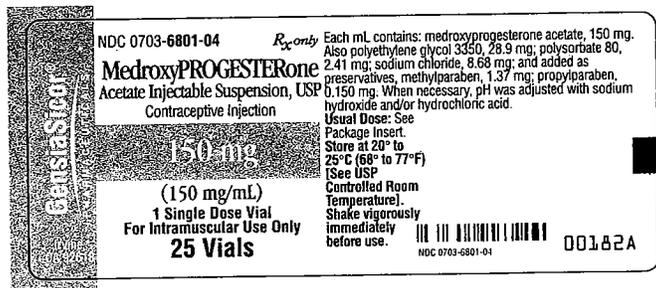
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