

DEPO PROVERA[®]

Medroxyprogesterone Acetate USP, 150 mg/ml injection

Presentation

DEPO PROVERA is a white aqueous suspension containing medroxyprogesterone acetate USP 150 mg/ml.

Uses

Actions

Medroxyprogesterone acetate (17 alpha-hydroxy-6 alpha-methylprogesterone acetate) is a progestogen and a derivative of progesterone.

Medroxyprogesterone acetate induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. Medroxyprogesterone acetate induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrous cycles. It is devoid of androgenic and oestrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs, increases serum growth hormone levels.

DEPO PROVERA has prolonged progestational effects when administered by intramuscular (IM) injection.

DEPO PROVERA suppresses the secretion of pituitary gonadotropins which, in turn, prevents follicular maturation producing long-term anovulation in the reproductive-aged woman. DEPO PROVERA suppresses the Leydig cell function in the male, i.e. suppresses endogenous testosterone product.

A single dose of 50 mg of parenteral medroxyprogesterone acetate has the equivalent effect of 20 mg of oral progesterone given daily for 10 days in producing an optimal secretory change in an oestrogen-primed endometrium. This steroid also produces typical progestational changes in the cervical mucus (inhibits ferning) increases the viscosity of cervical mucus thereby increasing the difficulty of sperm penetration of the cervical mucus and increases the intermediate cell count in the maturation index of the vaginal epithelium.

Anti-cancer activity of DEPO PROVERA at pharmacologic doses may be dependent on its effect on the hypopituitary/gonadal axis oestrogen receptors and the metabolism of steroids at the tissue level.

Like progesterone parenteral medroxyprogesterone acetate is thermogenic. Clinically, suppression of adrenocortical function has not been observed at the dose levels employed for

ovulation suppression. However, at the very high dosage levels used in the treatment of certain cancers (500 mg daily or more) corticoid-like activity may manifest.

In chronic toxicity studies in rats and mice no significant differences between controls and treated groups in relation to clinical signs, mortality rates, development of neoplasms or the development of any other gross or histologic lesions developed. No teratogenic effects were observed in mice and rats. In rabbits DEPO PROVERA exhibited a corticoid-like effect on foetal development.

In long-term toxicology studies in monkeys two of the monkeys receiving intramuscular doses of 150 mg/kg every 90 days developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg or placebo every 90 days.

The occurrence of the lesions in these two monkeys does not signify that DEPO PROVERA is carcinogenic in women. The incidence of endometrial carcinoma reported with women on DEPO PROVERA is considerably less than the random incidence in the general population. This may be an artifact but it suggests no causal relationship between endometrial cancer and the usage of DEPO PROVERA. DEPO PROVERA is used successfully as palliative treatment in endometrial and breast cancer.

Pharmacokinetics

Parenteral medroxyprogesterone acetate is a long acting progestational steroid. The 150 mg/ml formulation reaches half its initial concentration in about 27 days. Its long duration of action results from its slow absorption from the injection site.

The principal metabolite of medroxyprogesterone acetate that has been identified is a 6alpha-methyl-6beta 17alpha, 21-trihydroxy-4-pregnene-3, 20-dione-17-acetate which is excreted in the urine.

Clinical Trials

Bone Mineral Density (BMD) Changes in Adult Women

In a controlled, clinical study adult women using DEPO PROVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD 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 -2.9%, -4.1%, -4.9%, -4.9% and -5.4% 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 (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. (See Warnings and Precautions.)

BMD Changes in Adolescent Females (12-18 years)

Preliminary results from an ongoing, open-label clinical study of DEPO PROVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that DEPO PROVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period. (See Warnings and Precautions.)

Indications

DEPO PROVERA is indicated for:

1. Ovulation suppression
2. The treatment of endometriosis
3. Adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma
4. The treatment of hormonally-dependent recurrent breast cancer in post-menopausal women

Ovulation suppression and Endometriosis

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO PROVERA, particularly if treated long-term (greater than 2 years), women should be assessed for risk factors for low bone mineral density including a review of their medical history, to determine the risk of developing osteoporosis. This should be conducted before the commencement of treatment. A careful re-evaluation of the risks and benefits of treatment beyond 2 years should be carried out in those patients who need to remain on DEPO PROVERA. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see Warnings and Precautions).

Dosage and Administration

Ovulation Suppression

DEPO PROVERA injectable suspension should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension. The intramuscular suspension is not formulated for subcutaneous injection.

The recommended dose is 150mg of DEPO PROVERA injectable suspension every three months administered by intramuscular injection in the gluteal or deltoid muscle. The initial injection should be given during the first 5 days after the onset of a normal menstrual period; within 5 days post-partum if not breast-feeding; or if exclusively breast-feeding at or after six weeks post-partum.

It is recommended that physicians or others directly responsible for these patients advise them at the beginning of treatment that their menstrual cycle may be disrupted, that irregular and unpredictable bleeding or spotting are produced, but that this usually decreases to the point of amenorrhoea as treatment with DEPO PROVERA continues without other therapy being required.

Pfizer do not recommend routine or long-term cyclic use of supplemental oestrogens with DEPO PROVERA. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral oestrogens in the equivalent of 0.05 to 0.1 mg ethinyloestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

Based on limited experience, some investigators favour the use of a second injection of DEPO PROVERA before 90 days to control troublesome bleeding. The third and subsequent injections should be administered at separate 90 day intervals.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology. Uterine curettage may be required on rare occasions.

Endometriosis

The recommended dose of DEPO PROVERA given intramuscularly is 50 mg weekly or 100 mg every 2 weeks for at least 6 months.

Endometrial and Renal Carcinoma

Doses of 500 mg to 1000 mg of DEPO PROVERA intramuscularly per week are recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilised, it may be possible to maintain improvement with 500 mg per week or less. DEPO PROVERA is not recommended as primary therapy, but as adjunctive and palliative treatment in advanced inoperable cases including those with recurrent or metastatic disease.

Breast Cancer

The recommended dosage schedule is DEPO PROVERA 500 mg to 1000 mg per day intramuscularly for 28 days. The patient should then be placed on a maintenance schedule of 500 mg twice weekly as long as she is responding to treatment. Response to hormonal therapy (DEPO PROVERA) for breast cancer may not be evident until 8 to 10 weeks of therapy. Treatment with DEPO PROVERA should be terminated should rapid progression of disease occur at any time during therapy.

Women should be assessed for risk factors for low bone mineral density (BMD) when treated for ovulation suppression or endometriosis. If these are found to be present, a full risk-benefit evaluation should be undertaken by the prescriber to determine the appropriateness of using DEPO-PROVERA. In women with significant lifestyle and /or medical risk factors for osteoporosis, other methods of contraception should be considered prior to use of DEPO PROVERA.

BMD should also be evaluated when considering continuing DEPO PROVERA for contraception or treatment of endometriosis beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO PROVERA long-term for oncology indications.

Contraindications

- Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions.
- Known or suspected pregnancy.
- Missed abortion.
- Undiagnosed vaginal bleeding.
- Known or suspected malignancy of the breast (when used for ovulation suppression or gynaecology indications).
- Undiagnosed breast pathology.
- Undiagnosed urinary tract bleeding.
- Severe uncontrolled hypertension.
- Severe liver dysfunction.
- Known hypersensitivity to medroxyprogesterone acetate or any component of the drug.

Warnings

- **Thromboembolic Disorders:** DEPO PROVERA has not been causally associated with the induction of thrombotic or thromboembolic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis), however, medroxyprogesterone acetate is not recommended in any patient with a history of venous thromboembolism (VTE). The physician should be alert to the earliest manifestations of thrombotic or thromboembolic disorders. Should any of these occur or be suspected, the drug should be discontinued immediately.
- **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 papilloedema or retinal vascular lesions, medication should not be readministered.
- **Bleeding Irregularities:** Most women using DEPO PROVERA injectable suspension experience disruption of menstrual bleeding patterns following the administration of either a single or multiple injectable doses of medroxyprogesterone acetate (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding). If unexpected vaginal bleeding occurs or abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continue using DEPO PROVERA injectable suspension, fewer experience irregular bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-PROVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-PROVERA.

- **Loss of Bone Mineral Density (BMD):**

Contraception and Endometriosis: Use of DEPO PROVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen level. Decreases in serum oestrogen due to DEPO PROVERA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO PROVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after DEPO PROVERA is discontinued and ovarian oestrogen production increases. A study to assess the reversibility of loss of BMD in adolescent females is ongoing.

DEPO PROVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO PROVERA long term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO PROVERA long-term (greater than 2 years) a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered. (See Uses, Clinical Trials)

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO PROVERA in women with osteoporotic risk factors such as:

- Chronic alcohol and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- Low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- Metabolic bone disease
- Strong family history of osteoporosis

Oncology: There are no studies on the bone mineral density (BMD) effects of high doses of parenteral DEPO PROVERA for oncology use.

However, 2 clinical studies of adult women of childbearing potential and of adolescent females given DEPO-PROVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-PROVERA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some cancer patients who use DEPO PROVERA long term.

It is recommended that all patients have adequate calcium and vitamin D intake.

- **Cancer risks:**

Long-term case-controlled surveillance of users of DEPO PROVERA injectable suspension found slight or no increased overall risk of breast cancer and no overall increased risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-PROVERA use.

The overall relative risk of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-PROVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1) in women aged less than 25 years with more than 2 years exposure to DEPO-PROVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A Relative Risk of 2.19 thus increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-PROVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk 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 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Additional precautions for oncology patients

- Medroxyprogesterone acetate may produce cushingoid symptoms.
- Some patients receiving high dose medroxyprogesterone acetate used in the treatment of cancer, may exhibit suppressed adrenal function. Medroxyprogesterone acetate may

decrease ACTH and hydrocortisone blood levels. Animal studies show that medroxyprogesterone acetate possesses adrenocorticoid activity.

- **Accidental Pregnancies:** Infants from unintentional pregnancies that occur 1-2 months after injection of DEPO PROVERA may be at increased risk of low birth weight, which in turn, is associated with an increased risk of neonatal death. Because there is a low incidence of pregnancies in women on medroxyprogesterone acetate, the attributable risk is low. There is no definitive information for the other formulations of medroxyprogesterone acetate.

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

- **Ectopic Pregnancy:** As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA who become pregnant or complain of severe abdominal pain.
- **Sexually Transmitted Diseases:** DEPO-PROVERA 150 mg/1 mL is intended to prevent pregnancy. Patients should be counselled that DEPO PROVERA injectable suspension does not protect against HIV infections (AIDS) or other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.
- In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation
- Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with intramuscular medroxyprogesterone acetate.
- **Laboratory Tests:** The physician/laboratory should be informed that the use of DEPO PROVERA may decrease the levels of the following endocrine biomarkers or affect the following laboratory tests:
 - Plasma/urinary steroids (e.g. cortisol, oestrogen, pregnanediol, progesterone, testosterone)
 - Plasma/urinary gonadotrophins (e.g. LH and FSH)
 - Sex-hormone-binding-globulin.
 - Glucose Tolerance Test
 - Metyrapone Test - the use of DEPO PROVERA may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of adrenal cortex to respond to ACTH should be demonstrated before metyrapone is administered.
 - Coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

Precautions

- **Physical Examination:** A complete medical and family history should be taken before the initiation of any hormone therapy. The pre-treatment and periodic physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology (Papanicolaou smear).
- **Fluid Retention:** DEPO PROVERA may cause some degree of fluid retention, therefore, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction.
- **Breakthrough Bleeding:** Unexpected vaginal bleeding during therapy with DEPO PROVERA should be investigated. Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.
- **Carbohydrate Metabolism:** Some patients receiving DEPO PROVERA may exhibit a decreased glucose tolerance. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving such therapy.
- **CNS Disorders and Convulsions:** Patients with a history of treatment for clinical depression should be carefully monitored while receiving DEPO PROVERA therapy and the drug discontinued if the depression recurs to a serious degree.
- **Weight Changes:** There was a tendency for women to gain weight while on therapy with medroxyprogesterone acetate. From an initial average body weight of 61.8 kgs (136 lbs) women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kgs (5.4 lbs). Women who completed 2 years of therapy gained an average of 3.68 kgs (8.1 lbs). Women who completed 4 years gained an average of 6.3 kgs (13.8 lbs). Women who completed 6 years gained an average of 7.5 kgs (16.5 lbs). Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.
- **Return of Fertility:** DEPO PROVERA injectable suspension (150 mg intramuscular injection) has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% 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 and were lost to follow-up or changed their mind.
- **Liver Function:** Certain endocrine and possible liver function tests may be affected by treatment with DEPO-PROVERA. Therefore, if such tests are abnormal in a patient taking DEPO-PROVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister the drug.

- **Patient Age:** The age of the patient constitutes no absolute limiting factor, although treatment with progestins may mask the onset of the climacteric.
- **Pathology Tests:** The pathologist (laboratory) should be informed of the patient's use of DEPO PROVERA if endometrial or endocervical tissue is submitted for examination.
- **IM Administration:** Gluteal infiltration and abscess formation may occur with intramuscular administration.
- Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-PROVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

Use in Pregnancy (Category D)

DEPO PROVERA is contraindicated in women who are pregnant.

Studies in animals have shown that progestogens, including medroxyprogesterone acetate, may have an adverse effect on the developing foetus, including teratogenicity and foetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female foetus.

Some 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 (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female foetus and because of the increased association of hypospadias in the male foetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children 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.

DEPO-PROVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If DEPO PROVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the foetus.

To ensure that DEPO-PROVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first five days after the onset of a normal menstrual period
- within five days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy

When switching from other contraceptive methods, MPA IM 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 MPA within 7 days after taking their last active pill).

Use in Lactation

Medroxyprogesterone acetate and its metabolites are excreted in breast milk. In mothers who are breastfeeding and who are treated with DEPO PROVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty and there is no evidence to suggest that this presents any hazard to the nursing child.

Use in Children

DEPO PROVERA is not indicated before menarche. Data are available in adolescent females (12-18 years) (see Uses, *Clinical Trials*). Other than concerns about loss of BMD, the safety and effectiveness of DEPO PROVERA are expected to be the same for postmenarcheal adolescent and adult females.

Use in Hepatic Insufficiency

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of medroxyprogesterone acetate. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolized in patients with severe liver insufficiency, (See Contraindications).

Use in Renal Insufficiency

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of medroxyprogesterone acetate. However, since medroxyprogesterone acetate is almost exclusively eliminated by hepatic metabolism, no dosage adjustment should be necessary in women with renal insufficiency.

Adverse Effects

Body System	Event
Genitourinary	Abnormal uterine bleeding (irregular, increase, decrease), amenorrhoea, alterations of cervical secretions, cervical erosions, changes in the position of the transformation zone, leukorrhoea, pelvic pain, prolonged anovulation, vaginitis
Breast	Galactorrhea, mastodynia, tenderness
Central Nervous System	Convulsions, confusion, depression, dizziness, euphoria, fatigue, headache, insomnia, loss of concentration, nervousness, somnolence, vision disorders
Gastrointestinal/Hepatobiliary	Abdominal pain or discomfort, bloating, cholestatic icterus/jaundice, constipation, diarrhoea, dry mouth, disturbed liver function (transient elevations of alkaline phosphatase and/or serum transaminase activities), nausea, vomiting
Metabolic & Nutritional	Adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), corticoid-like effects (e.g., Cushingoid syndrome), decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
Cardiovascular	Cerebral and myocardial infarction, congestive heart failure, increased blood pressure, palpitations, pulmonary embolism, retinal thrombosis, tachycardia, thromboembolic disorders, thrombophlebitis
Haematological	Elevation of white blood cells and platelet counts
Skin & Mucous Membranes	Acne, alopecia, hirsutism, pruritus, rash, urticaria
Allergy	Hypersensitivity reactions (e.g., anaphylaxis & anaphylactoid reactions, angioedema)
Musculoskeletal	Arthralgia, asthenia, backache, injection-site reactions, gluteal filtration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e. greater than 2.5 mL), leg cramps, loss of bone mineral density
Miscellaneous	Changes in specific appetite, changes in libido or anorgasmia, oedema/fluid retention, hot flushes, hypercalcaemia, hyperkalaemia, malaise, pyrexia, weight change

In a clinical trial conducted using DEPO-PROVERA for contraception, 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 following adverse reactions were reported by more than 5% of subjects:

- Menstrual irregularities (bleeding &/or amenorrhoea)
- Abdominal pain or discomfort
- Dizziness
- Weight changes
- Nervousness
- Headache
- Asthenia (weakness or fatigue)

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

- Decreased libido or anorgasmia
- Vaginitis
- Backache
- Pelvic pain
- Leg cramps
- Breast pain
- Depression
- No hair growth or alopecia
- Nausea
- Bloating
- Insomnia
- Rash
- Leukorrhoea
- Oedema
- Acne
- Hot flushes

Events reported by fewer than 1% of subjects included: galactorrhoea, melasma, chloasma, convulsions, changes in appetite, gastrointestinal disturbances, jaundice, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive sweating and body odour, 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, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO PROVERA.

Interactions

Aminoglutethimide administered concomitantly with high doses of medroxyprogesterone acetate may significantly depress the serum concentrations of medroxyprogesterone acetate. Users of DEPO PROVERA should be warned of the possibility of decreased efficacy with the use of aminoglutethimide or any related drugs.

Overdosage

No serious medical effects have been reported in association with overdosage of DEPO-PROVERA (medroxyprogesterone acetate) injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

Contact the Poisons Information Centre for advice on the management of an overdose.

Pharmaceutical Precautions

Syringe: Store at or below 25°C.

Vial: Store below 30°C.

Medicine Classification

Prescription Medicine.

Package Quantities

150 mg/mL - 1 mL disposable syringe

150 mg/mL - 1 mL vial.

Further Information

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

Method	Lowest Expected	Typical
Injectable progestogen DEPO PROVERA	0.3	0.3
Implants Norplant (6 capsules)	0.2	0.2
Female sterilisation	0.2	0.4
Male sterilisation	0.1	0.15
Pill		3
Combined	0.1	
Progestin only	0.5	
IUD		3
Progestasert	2.0	
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 al

* Lowest expected - when used exactly as directed.

Typical - includes those not following directions exactly.

Depo-Provera contains the following excipients: hydrochloric acid, macrogol 3350, polysorbate 80, sodium chloride, methyl 4-hydroxybenzoate, propyl hydroxybenzoate, sodium hydroxide and water for injection.

Name and Address

Pfizer New Zealand Ltd
PO Box 3998
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Toll Free Number: 0800 736 363

Date of Preparation

20 August 2010

DEPO-PROVERA is a registered trademark.