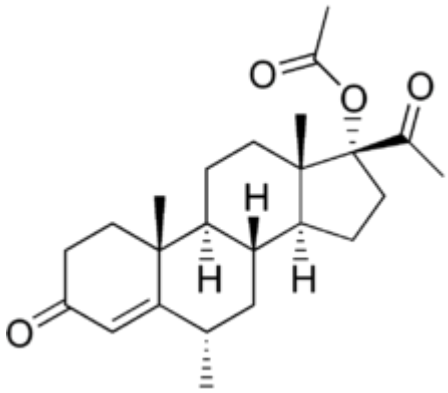
PRODUCT INFORMATION

DEPO-PROVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA) is 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate, the molecular formula is $C_{24}H_{34}O_4$ and its molecular weight is 386.52. The structural formula is as follows:



DESCRIPTION

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

Animal

MPA 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. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-PROVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-PROVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-PROVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-PROVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-PROVERA.

Pharmacokinetics

Absorption

Parenteral MPA is a long-acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-PROVERA, MPA levels 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 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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 bone mineral density (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 PRECAUTIONS.

BMD changes in adolescent females (12 to 18 years)[4,5]

An open-label non-randomised clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in

lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued and hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued (see PRECAUTIONS).

INDICATIONS

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women, who use DEPO-PROVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see PRECAUTIONS).[6]

CONTRAINDICATIONS

DEPO-PROVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see DESCRIPTION)
- known or suspected pregnancy (see PRECAUTIONS, Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

PRECAUTIONS

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Ocular disorders

Discontinue medication pending examination if there is 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 be withdrawn.

Bleeding irregularities

Most women receiving DEPO-PROVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If 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 continued to use DEPO-PROVERA, fewer experienced intermenstrual 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.[7]

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.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-PROVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. 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 adult females, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to be fully reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases.[6] Full recovery took 1 year at the lumbar spine and approximately 3 years for total hip after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see CLINICAL TRIALS, BMD changes in adolescent females (12 to 18 years)).

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.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] Since loss of 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.[6]

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.

See CLINICAL TRIALS.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, two 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 estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] 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 RR of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89)[6] 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 RR increases in women aged between 25 and 34 years of age (RR of 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.[15] The risk of

breast cancer[10] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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 RR 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 RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-PROVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[17,18]

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 preconceptual exposure to DEPO-PROVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[19]

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare 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/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and 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.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

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

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-PROVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-PROVERA 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 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 DEPO-PROVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see DOSAGE AND ADMINISTRATION).

General

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.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in pregnancy: Category D

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

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

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

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 (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 fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

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 fetus.

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 5 days after the onset of a normal menstrual period
- within 5 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).

See DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA. 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. No adverse effects have been noted.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for post-menarcheal adolescent and adult females. [6]

Use in hepatic impairment

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

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of MPA.[20] DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

ADVERSE EFFECTS

The following events are associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: Palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

Eye disorders: Retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal: Abdominal distension, nausea, constipation, diarrhoea, dry mouth.

General disorders and administrative site conditions: Fatigue, injection site reactions, malaise, hyperpyrexia.

Hepatobiliary disorders: Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorders: Anaphylactic reactions, anaphylactoid reactions, angioedema.

Investigations: Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.

Metabolic and nutritional disorders: Exacerbation of diabetes mellitus, hypercalcaemia.

Musculoskeletal and connective tissue disorders: Arthralgia, gluteal infiltration 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), back pain, muscle spasm.

Nervous System disorders: Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

Reproductive and breast disorders: Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

Skin and subcutaneous tissue disorders: Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- 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/fluid retention
- acne
- hot flushes.

The following events were reported by fewer than 1% of subjects

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.

Hepatobillary disorders: Jaundice, jaundice cholestatic.

Immune systems disorders: Drug hypersensitivity reactions.

Metabolism and nutrition disorders: Changes in appetite.

Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.

Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.

Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.

Renal and urinary disorders: Genitourinary infections.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.

Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.

Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.

Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

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.[21,22,23]

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

DOSAGE AND ADMINISTRATION

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[8]

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-PROVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol 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.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

OVERDOSAGE

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

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA 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 on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

DEPO-PROVERA 150 mg/mL injection suspension is supplied as:

- 1 x 1 mL vial
- 1 x 1 mL syringe.[#]

[#]This presentation is not currently available in Australia.

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 August 1991.

DATE OF MOST RECENT AMENDMENT

07 March 2017.

® Registered trademark

REFERENCES

1. Trussell J, Hatcher RA, Cates W Jr, Stewart FH, Kost K. A guide to interpreting contraceptive efficacy studies. Obstet Gynaecol 76:558-567, 1990.
2. Trussell J, Kost K. Contraceptive failure in the United States: A critical review of the literature. Stud Fam Plan 18:237-283, 1987.
3. Skillern L, Hilton C. Final Study Report Protocol M5400/0234: Assessment of Bone Mineral Density in Women Receiving DEPO-PROVERA Contraceptive Injection. 18 February 04 Pfizer Inc.
4. D'Angelo P, Wajszczuk C. Interim Statistical Report DEPO-PROVERA: Evaluation of Bone Mineral Density and Total Body Calcium in Adolescent DP150CI Users and

Nonhormonal Contraceptive Users. May 2003 internal study report for on-going study Z/5400/0261; conducted under US-IND 45,275.

5. Interim Statistical Report for study Z/5400/0261, dated May 04.
6. Wolter KD. Clinical Overview to Support Bone Mineral Density Revisions dated Sep04 Pfizer Inc.
7. Schwallie PC, Assenzo JR. Contraceptive use-efficacy study utilizing medroxyprogesterone acetate administered as an intramuscular injection once every 90 days. Fertil Steril 24:331-339, 1973.
8. Wolter KD. Clinical Overview to Support Bone Mineral Density Revisions for Oral and High Dose Parenteral Formulations. Dated Oct04, Pfizer Inc.
9. Looker AC. Dietary Supplement Use in Women: Current Status and Future Directions. Amer Soc of Nutr Sci 002213166/2003 1987S-1991S.
10. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Breast cancer and depot-medroxyprogesterone acetate: A multi-national study. Lancet 338:833-838, 1991.
11. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. Int J Cancer 49:191-95, 1991.
12. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of liver cancer. Int J Cancer 49:182-185, 1991.
13. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. Contraception 45:299-312, 1992.
14. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. Int J Cancer 49:186-190, 1991.
15. Paul C, Skegg DC, Spears GF. Depo-medroxyprogesterone (DEPO-PROVERA) and risk of breast cancer. BMJ 299: 759-62, 1989.
16. Australian Institute of Health & Welfare, Australasian Association of Cancer Registries. Cancer in Australia 1983-1985. Cancer Series Number 1.
17. Gray, RH, Pardthaisong T. In Utero Exposure to Steroid Contraceptives and Survival During Infancy. Am J Epidemiol 134:804-811, 1991.
18. Pardthaisong T, Gray RH. In Utero Exposure to Steroid Contraceptives and Outcome of Pregnancy. Am J Epidemiol 134:795-803, 1991.
19. Pardthaisong T, Gray RH, McDaniel EB, Chandacham A. Steroid Contraceptive Use and Pregnancy Outcome. Teratology 38:51-58, 1988.
20. Van Deijk WA, Bitjham GH, Mellink WAM, and Meulenberg PMM. Influence of Aminoglutethimide on Plasma Levels of Medroxyprogesterone Acetate: Its Correlation with Serum Cortisol. Cancer Treatment Reports 69:1, 85-90, January 1985.
21. Gupta A, Donaldson A. A Review of Medroxyprogesterone Cases Reporting Decreased Bone Mineral Density Events, 18 August 2004, Pfizer Inc.

22. Gupta A, Donaldson A. A Review of Medroxyprogesterone Cases Reporting Decreased Fracture Events, 18 August 2004, Pfizer Inc.

23. Gupta A, Donaldson A. A Review of Pfizer's Legacy Safety Database for Non-Clinical Medroxyprogesterone Cases Reporting Fractures-Events or Decreased Bone Mineral Density-Events. Dated 7 October 2004, Pfizer Inc.