NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DEPO-PROVERA® 150 mg/mL Injection (depot)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL vial contains 150 mg/mL Medroxyprogesterone acetate

Each 1 mL disposable syringe contains 150 mg/mL Medroxyprogesterone acetate

Excipients with known effects:

- Sodium
- Methyl hydroxybenzoate,
- Propyl hydroxybenzoate,

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DEPO-PROVERA 150 mg/mL Injection (depot) is a white, aqueous, suspension containing medroxyprogesterone acetate (MPA) as the active ingredient.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEPO-PROVERA is indicated for:

- ovulation suppression.

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 BMD 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 BMD (see section 4.4).

- the treatment of endometriosis.
- adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma.
- the treatment of hormonally-dependent recurrent breast cancer in post-menopausal women.

4.2 Dose and method of administration

Ovulation suppression

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

The recommended dose is 150 mg of DEPO-PROVERA every 3 months administered by IM 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 6 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.

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.

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 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.

Paediatric population

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see section 5.1, Clinical trial data). 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 MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see section 4.3).

Use in renal insufficiency

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

4.3 Contraindications

DEPO-PROVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- known or suspected pregnancy (see section 4.4)
- 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 MPA or any component of the injection (see section 6.1).

4.4 Special warnings and precautions for use

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, MPA 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.

Meningioma

Meningiomas have been reported following long-term administration of MPA (see Section 5.1). Patients treated with MPA should be monitored for signs and symptoms of meningiomas in accordance with clinical practice.

If a patient treated with MPA for a non-oncological indication is diagnosed with meningioma, MPA should be discontinued. Caution is advised when recommending MPA to patients with a history of meningioma.

If a patient treated with MPA for oncological indication is diagnosed with meningioma, the need for further treatment with MPA should be carefully considered on a case-by-case basis taking into account individual benefits and risks. Caution is advised when recommending MPA to patients with a history of meningioma.

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 experience disruption of menstrual bleeding patterns following the administration of either a single or multiple doses of MPA (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 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 BMD

Contraception and endometriosis

Use of DEPO-PROVERA reduces serum estrogen levels in premenopausal women and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. 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.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of DEPO-PROVERA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases. After discontinuing Depo-Provera injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck (see section 5.1, Clinical trial data).

In adults, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see section 5.1, Clinical trial data). A large observational study of female contraceptive users showed that use of Depo-Provera injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures (see section 5.1, Clinical trial data).

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 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 section 5.1, Clinical trial data).

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 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 section 5.1, Clinical trial data). 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.

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 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 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) 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. 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 of 20.97/100,000 in Australian women, aged 30 to 34 years. A RR of 2.19 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 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

MPA may produce cushingoid symptoms.

Some patients receiving high dose MPA, used in the treatment of cancer, may exhibit suppressed adrenal function. MPA may decrease ACTH and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Accidental pregnancies

Infants from unintentional pregnancies that occur 1 to 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 MPA, the attributable risk is low. There is no definitive information for the other formulations of MPA.

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.

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 infections

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DEPO-PROVERA does not protect against sexually transmitted infections (STIs) including HIV infections (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

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

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

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 MPA. 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 (150 mg IM 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 progestogens 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 IM 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.

4.5 Interaction with other medicines and other forms of interaction

Aminoglutethimide administered concomitantly with high doses of MPA may significantly depress the serum concentrations of MPA. Users of DEPO-PROVERA should be warned of the possibility of decreased efficacy with the use of aminoglutethimide 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 of MPA with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration of MPA with CYP3A4 inhibitors may increase MPA levels.

Effects on 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, estrogen, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D

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

DEPO-PROVERA is contraindicated in women who are pregnant.

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.

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 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).

Lactation

MPA 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.

4.7 Effects on ability to drive and use machines

The effect of medroxyprogesterone acetate on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable effects

Body System	Event
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), amenorrhoea, galactorrhoea, cervical discharge, uterine cervical erosion, changes in the position of the transformation zone, vaginal

Body System	Event
	discharge, pelvic pain, breast pain, breast tenderness, vaginitis.
Psychiatric disorders	Depression, insomnia, nervousness, anorgasmia, changes in libido, libido decreased, confusion, euphoria.
Endocrine disorders	Corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.
Nervous system disorders	Seizure, cerebral infarction, dizziness, headache, loss of concentration, somnolence, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremors.
Eye disorders	Retinal embolism and thrombosis, diabetic cataract, visual impairment.
Vascular disorders	Embolism and thrombosis, hot flush, thrombophlebitis.
Gastrointestinal disorders	Abdominal pain, abdominal discomfort, abdominal distension, constipation, diarrhoea, dry mouth, nausea, vomiting.
Hepatobiliary disorders	Liver disorder, jaundice cholestatic, jaundice, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).
Metabolism and nutritional disorders	Diabetes mellitus exacerbated, hypercalcaemia, hyperkalaemia, increased appetite, weight fluctuation.
Cardiac disorders	Myocardial infarction, cardiac failure congestive, palpitations, tachycardia.
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism.
Skin and subcutaneous tissue disorders	Acne, alopecia, hirsutism, pruritus, rash, urticaria, hyperhidrosis.
Immune system disorders	Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, angioedema.
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, 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), muscle spasms.
Renal and urinary system disorders	Glycosuria.
General disorders and administration site conditions	Oedema, fluid retention, malaise, pyrexia, asthenia, fatigue, injection-site reaction.
Investigations	Bone density decreased, glucose tolerance decreased, weight increased, weight decreased, blood pressure increased, liver function test abnormal, white blood cell count increased, platelet count increased.

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 &/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.

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.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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

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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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. It is devoid of androgenic and estrogenic 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 MPA has the equivalent effect of 20 mg of oral progesterone given daily for 10 days in producing an optimal secretory change in an estrogen-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 estrogen receptors and the metabolism of steroids at the tissue level.

Like progesterone parenteral MPA 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 fetal development.

In long-term toxicology studies in monkeys, 2 of the monkeys receiving IM 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 2 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.

Clinical trial data

BMD changes in adult women

In a non-randomised controlled, clinical study comparing adult women using DEPO-PROVERA (150 mg IM) for up to 5 years to women who elected to use no hormonal contraception, 42 DEPO-PROVERA users completed 5 years of treatment and provided at least 1 follow-up BMD measurement after stopping DEPO-PROVERA. Among DEPO-PROVERA users, BMD declined during the first 2 years of use, with little 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. There were no significant changes in BMD in the control women over the same period of time.

BMD recovery post-treatment in adult women

In the same study population there was partial recovery of BMD toward baseline values during the 2-year period after stopping use of DEPO-PROVERA (150 mg IM).

After 5 years of treatment with DEPO-PROVERA (150 mg IM), the mean % change in BMD from baseline was -5.4%, -5.2% and -6.1% at the spine, total hip and femoral neck, respectively, while untreated control women, over the same time interval, showed mean changes from baseline of +/- 0.5% or less at the same skeletal sites. Two years after stopping DEPO-PROVERA, mean BMD had increased at all 3 skeletal sites but deficits remained: -3.1%, -1.3% and -5.4% at the spine, total hip and femoral neck, respectively. At the same time point, women in the control group showed mean changes from baseline BMD of 0.5%, 0.9% and -0.1% at the spine, total hip and femoral neck, respectively.

BMD changes in adolescent females (12 to 18 years)

The effect of DEPO-PROVERA (150 mg IM) use on BMD for up to 240 weeks (4.6 years) was evaluated in an open-label non-comparative clinical study of 159 adolescent females (12-18 years) who elected to begin treatment with DEPO-PROVERA; 114 of the 159 participants used DEPO-PROVERA continuously (4 injections during each 60-week period) and had BMD measured at Week 60. BMD declined during the first 2 years of use with little change in subsequent years. After 60 weeks of DEPO-PROVERA use, mean % BMD changes from baseline were -2.5%, -2.8% and -3.0% at the spine, total hip and femoral neck, respectively. A total of 73 subjects continued to use DEPO-PROVERA through 120 weeks; mean % BMD changes from baseline were -2.7%, -5.4% and -5.3% at the spine, total hip and femoral neck, respectively. A total of 28 subjects continued to use DEPO-PROVERA through 240 weeks; mean % BMD changes from baseline were -2.1%, -6.4% and -5.4% at the spine, total hip and femoral neck, respectively.

BMD recovery post-treatment in adolescents

In the same study, 98 adolescent participants received at least 1 DEPO-PROVERA injection and provided at least 1 follow-up BMD measurement after stopping DEPO-PROVERA use, with DEPO-PROVERA treatment for up to 240 weeks (equivalent to 20 DEPO-PROVERA injections) and post-treatment follow-up extending for up to 240 weeks after the final DEPO-PROVERA injection. The median number of injections received during the treatment phase was 9. At the time of the final DEPO-PROVERA injection, BMD % changes from baseline were -2.7%, -4.1% and -3.9% at the spine, total hip and femoral neck, respectively. Over time these mean BMD deficits fully recovered after DEPO-PROVERA was discontinued. Full recovery required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck. Longer duration of treatment and smoking were associated with slower recovery (see section 4.4, *Loss of BMD*).

Relationship of fracture incidence to use of DEPO-PROVERA (150 mg IM) or non-use by women of reproductive age

A retrospective cohort study to assess the association between DEPO-PROVERA and the incidence of bone fractures was conducted in 312,395 female contraceptive users in the UK. The incidence rates of fracture were compared before and after DEPO-PROVERA use started and also between DEPO-PROVERA users and women who used other contraceptives but had no recorded use of DEPO-PROVERA. Among women using DEPO-PROVERA, use of DEPO-PROVERA was not associated with an increase in fracture risk (incident rate ratio [IRR] = 1.01, 95% CI 0.92-1.11, comparing the study follow-up period with up to 2 years of observation prior to DEPO-PROVERA use). However, DEPO-PROVERA users did have more fractures than non-users not only after first contraceptive use (IRR = 1.23, 95% CI 1.16-1.30), but also before first contraceptive use (IRR = 1.28, 95% CI 1.07-1.53).

In addition, fractures at the specific bone sites characteristic of osteoporotic fragility fractures (spine, hip, pelvis) were not more frequent among DEPO-PROVERA users compared to non-users (IRR = 0.95, 95% CI 0.74-1.23), nor was there any evidence that longer use of DEPO-PROVERA (2 years or more) confers greater risk for fracture compared to less than 2 years of use.

These data demonstrate that DEPO-PROVERA users have an inherently different fracture risk profile to non-users for reasons not related to DEPO-PROVERA use.

Maximum follow-up in this study was 15 years, therefore, possible effects of DEPO-PROVERA that might extend beyond 15 years of follow-up cannot be determined.

Accidental pregnancy rates

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**
Progestogen injection 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 Combined Progestogen only	 0.1 0.5	3
IUD Progestasert Copper T 380A	 2.0 0.8	3
Condom	2	12
Diaphragm	6	18
Cap	6	18
Spermicides	3	21
Sponge Parous women Nulliparous women	 9 6	 28 18
Periodic abstinence	1-9	20
Withdrawal	4	18
No method	85	85

* Lowest expected - when used exactly as directed; Typical - includes those not following directions exactly.

Meningioma

Based on results from a French epidemiological case-control study, an association between medroxyprogesterone acetate and meningioma has been observed. This study was based on data from the French national health data system (SNDS – Système National des Données de Santé) and included a population of 18,061 women who had intracranial surgery for meningioma and 90,305 women without meningioma. The exposure to medroxyprogesterone acetate 150 mg/3 mL injectable was compared between women who had intracranial surgery for meningioma and women without meningioma. Analyses showed an excess risk of meningioma with the use of medroxyprogesterone acetate 150 mg/3 mL (9/18,061 (0.05%) v

11/90,305 (0.01%), OR 5.55 (95% CI 2.27–13.56)). This excess risk seems to be driven primarily by prolonged use of medroxyprogesterone acetate.

Based on results from a matched case–control study from the United States, medroxyprogesterone acetate use was associated with increased odds of the presence of meningioma with evidence of increased odds with increasing duration of use. Data were obtained from the IBM MarketScan claims database for the years 2006–2022. A total of 117,503 cases and 1,072,907 matched controls were included in the analysis. For all meningiomas, the prevalence of oral exposure to medroxyprogesterone acetate was similar between cases (2.38%) and controls (2.29%). In both crude and adjusted models, medroxyprogesterone acetate exposure was not associated with being a case (adjusted OR 0.97, 95% CI 0.93–1.01); this null association persisted across all duration categories. The prevalence of injection exposure to medroxyprogesterone acetate was nearly twice as high among cases (0.67%) than controls (0.39%); medroxyprogesterone acetate exposure was associated with 76% increased odds of being a case (OR 1.76, 95% CI 1.63–1.90), an association that persisted in the adjusted model (OR 1.53, 95% CI 1.40–1.67). There was evidence of increased odds by duration of exposure (linear trend, $p < 0.0001$). This association was notably specific to injection exposure to medroxyprogesterone acetate and cerebral meningiomas. No association was observed for oral medroxyprogesterone acetate exposure or for spinal meningiomas (for both oral and injection medroxyprogesterone acetate exposure).

5.2 Pharmacokinetic properties

Parenteral MPA 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 MPA that has been identified is a 6α-methyl-6β,17α,21-trihydroxy-4-pregnene-3, 20-dione-17-acetate which is excreted in the urine.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid,
Macrogol 3350,
Methyl hydroxybenzoate,
Polysorbate 80,
Propyl hydroxybenzoate,
Sodium chloride,
Sodium hydroxide.

6.2 Incompatibilities

None stated.

6.3 Shelf life

Syringe: 60 months from date of manufacture

Vial: 36 months from date of manufacture

6.4 Special precautions for storage

Syringe: Store at or below 25°C.

Vial: Store below 30°C.

6.5 Nature and contents of container

150 mg/mL - 1 mL disposable syringe.

150 mg/mL - 1 mL vial.

6.6 Special precautions for disposal and other handling

None stated.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Ltd
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Auckland, New Zealand, 1140.
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9. DATE OF FIRST APPROVAL

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10. DATE OF REVISION OF THE TEXT

3 October 2025

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 & 5.1	Addition of new information regarding meningioma
4.9	Minor editorial change