

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medroxyprogesterone Acetate Injectable Suspension USP 150 mg/mL

Strength

Strength –150 mg/mL

Pharmaceutical Form

Form – Sterile Suspension for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Medroxyprogesterone Acetate USP: 150 mg.

Water for Injection USP: Q.S.

For the full list of excipients, see section **List of Excipients**.

3. PHARMACEUTICAL FORM

Suspension for Injection. White to off-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Suppression of ovulation (contraception).

Since loss of bone mineral density may occur in pre-menopausal women who use medroxyprogesterone acetate injections long-term (see section **Special warnings and precautions for use**), a risk/benefit assessment, which also takes into consideration the decrease in bone mineral density that occurs during pregnancy and/or lactation, should be considered.

4.2 Posology and method of administration

The recommended dose for the suppression of ovulation is 150 mg every three months, administered by deep, intramuscular injection into the gluteal or deltoid muscle. To increase assurance that the patient is not pregnant at the time of the first administration, this injection should be given during the first 5 days following a normal menstrual period; in the first 5 days postpartum if the patient is not breast-feeding; if the patient is breast-feeding, at or after 6 weeks postpartum. If the interval between the injections is greater than 13 weeks, physician should ensure that the patient is not pregnant before administering the product.

Doctors are recommended to warn the patient at the beginning of treatment that her menstrual cycle may be disturbed, that irregular unpredictable bleeding or spotting may occur but that this will diminish as treatment with Medroxyprogesterone acetate injectable suspension 150 mg/mL is continued and will finally result in amenorrhoea.

Excessive or prolonged bleeding which becomes a nuisance to the patient can generally be controlled by oral or parenteral administration of oestrogens, namely 0.05 to 0.1 mg of ethinyl oestradiol per day for 7 to 21 days. This treatment may be continued for 1 to 2 cycles, but should not be considered as a long-term treatment. Based on limited experience, some investigators are in favour of giving a second injection of Medroxyprogesterone acetate injectable suspension 150 mg/mL before 90 days, to control annoying bleeding. Following injections are administered at 90-day intervals. If abnormal bleeding persists, appropriate examinations should be performed to exclude the possibility of a pathological condition.

Switching from other methods of contraception to Medroxyprogesterone acetate injectable suspension 150 mg/mL: When switching from other contraceptive methods to Medroxyprogesterone acetate injectable suspension 150 mg/mL, the latter 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 to Medroxyprogesterone acetate injectable suspension 150 mg/mL should have their first injection of Medroxyprogesterone acetate injectable suspension 150 mg/mL within 7 days after taking their last active pill).

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

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.

Use in children:

The intramuscular injection of medroxyprogesterone acetate is not indicated before menarche.

Data are available in adolescent females (12-18 years) (see sections **Special warnings and Precautions for use** and **Pharmacodynamic properties**). Other than concerns about loss of bone mineral density, the safety and effectiveness of intramuscular injections of medroxyprogesterone acetate are expected to be the same for postmenarchal adolescent and adult females.

4.3 Contraindications

The use of Medroxyprogesterone acetate injectable suspension 150 mg/mL is contraindicated in the event of:

- Known hypersensitivity to medroxyprogesterone acetate or to any of the excipients.
- Undiagnosed vaginal bleeding
- Undiagnosed bleeding of the urinary tract
- Diagnosed or suspected breast cancer
- Active thrombophlebitis or a history of thromboembolism or cerebrovascular disease. Physicians should be alert to the manifestation of the first symptoms (thrombophlebitis, pulmonary embolism, cerebrovascular disease and retinal thrombosis)
- Pregnancy or suspected pregnancy
- Severe hepatic impairment or hepatic function disorders.

4.4 Special warnings and precautions for use

Loss of Bone Mineral Density:

Use of medroxyprogesterone acetate injection reduces serum estrogen levels in premenopausal women and is associated with significant loss of bone mineral density as bone metabolism accommodates to a lower estrogen level. This loss of bone mineral density 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 medroxyprogesterone acetate injections by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life. In both adult and adolescent females, the decrease in bone mineral density during treatment appears to be substantially reversible after

medroxyprogesterone acetate injections are discontinued and ovarian estrogen production increases(see section **Pharmacodynamic properties**: Studies on bone mineral density).

A retrospective cohort study to assess the effect of medroxyprogesterone acetate injections on the incidence of bone fractures was conducted in 312,395 female contraceptive users in Great Britain. The incidence rates of fracture were compared between depot medroxyprogesterone acetate users and contraceptive users who had no recorded use of depot medroxyprogesterone acetate. The incidence rate ratio (IRR) for any fracture during the follow-up period (mean = 5.5 years) was 1.41 (95% CI 1.35, 1.47). Among the sub-cohort with data before and after the first reported contraceptive treatment (N = 166,367), comparisons were made for the follow-up period and also for the 6-month period prior to first reported contraceptive treatment. Comparing depot medroxyprogesterone acetate users and non-users, the IRR for any fracture ‘before treatment’ (IRR 1.28, 95% CI 1.07, 1.53) was comparable to the IRR ‘after treatment’ (IRR 1.37, 95% CI 1.29, 1.45). The overall results support the conclusion that the higher observed incidence of fractures among depot medroxyprogesterone acetate users in this study was principally a result of factors other than exposure to depot medroxyprogesterone acetate.

Medroxyprogesterone acetate injections should only be used as a long-term (e.g. longer than 2 years) birth control method if other birth control methods are inadequate. Bone mineral density should be evaluated when a female needs to continue to use medroxyprogesterone acetate injections long term. In adolescent females, interpretation of bone mineral density results should take into account patient age and skeletal maturity.

Other birth control methods should be considered in the risk/benefit analysis for the use of medroxyprogesterone acetate injections in women with osteoporotic risk factors. Medroxyprogesterone acetate injections can pose an additional risk in patients with risk factors for osteoporosis (e.g. metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, marked family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids).

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

Breast cancer:

The use of combined oral oestrogens and progestogens by post-menopausal women has been reported to increase the risk of breast cancer. Results from a randomized placebo-controlled trial, the WHI (Women's Health Initiative) trial, and epidemiological studies have indicated an increased risk of breast cancer in women taking oestrogens/progestogens combinations for hormone therapy for several years. In the WHI trial on the combined use of conjugated equine oestrogens (CEE) and medroxyprogesterone acetate and in the observation studies, the excess risk increased with duration of use(see section **Posology and method of administration**). The combined use of oestrogens and progestogens has also been reported to result in an increase in abnormal mammograms requiring further evaluation.

In several epidemiological studies, no overall increased risk for breast cancer was found among women using long-acting injectable (depot) progestogens compared with women not using them. However, an increased relative risk (e.g. 2.0 in one study) was found for women who currently used long-acting injectable progestogens or had used them only a few years before. It is not possible to infer from these data whether this increased rate of breast cancer diagnosis among women using currently long-acting injectable progestogens was due to increased surveillance among these women, to the biological effects of these injectable progestogens or to a combination of reasons.

In case-control studies, long-term monitoring of Medroxyprogesterone acetate injectable suspension 150 mg/mL users has shown a slight increase or no increase in the overall risk of breast cancer and no increase in the overall risk of ovarian, cervical or liver cancer and has demonstrated the prolonged protective effect of a reduction in the risk of endometrial cancer in the user population. An increased relative risk of 2.19% (95% CI of 1.23 to 3.89) of breast cancer has been associated with taking Medroxyprogesterone acetate injectable suspension 150 mg/mL in women of less than 35 years old exposed to the drug for the first time in the 4 previous years. However, the overall relative risk for those who had used it over a long period was only 1.2% (95% CI of 0.96 to 1.52). Other recent analyses have shown similar results.

Before beginning treatment with Medroxyprogesterone acetate injectable suspension 150 mg/mL, the patient must undergo a thorough general examination during which any genital or mammary neoplasia must be excluded. This examination must be repeated each year. This

precaution does not concern patients in whom the treatment has been initiated for recurrent cancer of the endometrium, breast or kidneys.

Medroxyprogesterone acetate has not been causally associated with the induction of thrombotic or thromboembolic disorders, however medroxyprogesterone acetate is not recommended in any patient with a history of venous thromboembolism. Discontinuation of medroxyprogesterone acetate is recommended in patients who develop venous thromboembolism while undergoing therapy with medroxyprogesterone acetate.

Medroxyprogesterone acetate injectable suspension 150 mg/mL exerts a prolonged contraceptive effect. The mean time to conception for women who conceive is 10 months after the last injection, the range being from 4 to 31 months, and is not linked to the time during which the contraceptive has been used.

In the event of sudden onset of full or partial loss of vision or if proptosis, diplopia or migraine appears, Medroxyprogesterone acetate injectable suspension 150 mg/mL should not be re-administered before an examination is undertaken. Medroxyprogesterone acetate injectable suspension 150 mg/mL must be discontinued if the findings should reveal papilloedema or damage to the vessels of the retina.

Medroxyprogesterone acetate injectable suspension 150 mg/mL can cause weight gain and fluid retention. Caution must be exercised with patients suffering from conditions that could be negatively affected by these factors.

Most women using Medroxyprogesterone acetate injectable suspension 150 mg/mL present a pattern of disturbed menstrual bleeding, which may include irregular or unpredictable bleeding or spotting, or more rarely heavy or continuous bleeding. As treatment continues, fewer patients suffer irregular bleeding and more have amenorrhoea. In the case of breakthrough bleeding, as in all cases of irregular vaginal bleeding, organic causes must be considered.

Any unexpected vaginal bleeding during the treatment with Medroxyprogesterone acetate injectable suspension 150 mg/mL must be investigated. Routine or long-term cyclic use of additional oestrogens to control abundant or prolonged bleeding while using

Medroxyprogesterone acetate injectable suspension 150 mg/mL as a means of contraception is not recommended.

Patients with a history of mental depression must be carefully monitored during treatment with Medroxyprogesterone acetate injectable suspension 150 mg/mL. Some patients may complain of premenstrual type depression during treatment with Medroxyprogesterone acetate injectable suspension 150 mg/mL.

Patients should be informed that Medroxyprogesterone acetate injectable suspension 150 mg/mL does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

A decrease in glucose tolerance has been observed in some patients receiving progestogen treatment. Diabetic patients treated with progestogen should be closely monitored and antidiabetic treatment must be possibly adapted.

If jaundice develops, interrupting the treatment must be considered.

Since this product contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, it could cause allergic reactions (possibly delayed), and exceptionally bronchospasm.

Anatomical pathologists should be informed of the treatment with Medroxyprogesterone acetate injectable suspension 150 mg/mL whenever they are given endometrial and endocervical tissue samples for analysis.

The physician/laboratory must be informed of the fact that the use of Medroxyprogesterone acetate injectable suspension 150 mg/mL can lower the levels of the following endocrine biological markers:

- a. Plasma/urinary steroids (e.g. cortisol, oestrogen, pregnanediol, progesterone, testosterone)
- b. Plasma/urinary gonadotrophins (e.g. lutenising hormone and follicle stimulating hormone)
- c. Sex-hormone-binding globulin.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglutethimide administered concomitantly with high-dose medroxyprogesterone acetate may significantly depress the bioavailability of medroxyprogesterone acetate. Patients using high-dose medroxyprogesterone acetate should be warned of the possibility of decreased efficacy with the use of aminoglutethimide.

For interactions with certain laboratory tests, see the last paragraph of the previous section **Special warnings and precautions for use.**

4.6 Fertility, pregnancy and lactation

Medroxyprogesterone acetate is contra-indicated in pregnant women.

Some reports suggest an association between an intrauterine exposure to progestogen drugs in the first three months of pregnancy and genital abnormalities in male and female foetuses.

Children born from unexpected pregnancies occurring one to two months following injection of Medroxyprogesterone acetate injectable suspension 150 mg/mL may have a high risk of low birth weight, which is in turn associated with a higher risk of neonatal death.

The supposed risk is low because such pregnancies are uncommon.

The use of progestogens is not recommended for establishing a diagnosis of pregnancy.

Patients using medroxyprogesterone acetate during pregnancy or becoming pregnant while taking the medication must be warned of the potential danger to the foetus.

Medroxyprogesterone acetate and its metabolites are excreted in human milk. There is no evidence to indicate that this involves any risk for the lactating child.

4.7 Effects on ability to drive and use machines

Medroxyprogesterone acetate injectable suspension 150 mg/mL negligible influence on the ability to drive and use machines.

There are no known data regarding the effect on the ability to drive or operate machinery. In view of the pharmacological profile of medroxyprogesterone acetate no significant effect should be expected.

4.8 Undesirable effects

The following undesirable effects, classified by organ system, have been associated with the use of progestogens:

Urogenital system disorders	Irregular menstruation (bleeding and amenorrhoea or both), reduced libido or absence of orgasm, leucorrhoea, vaginitis, hot flushes, pelvic pain, abnormal uterine bleeding (irregular, increase, reduction) and prolonged anovulation.
Breast disorders	Breast sensitivity, mastodynia and galactorrhoea.

Central nervous system disorders	Nervousness, insomnia, drowsiness, fatigue, depression, dizziness, headaches, convulsions.
Gastrointestinal and hepatobiliary disorders	Nausea, abdominal pain or discomfort, sensation of bloating, hepatic function disorders, jaundice.
Metabolism and nutrition disorders	Reduced glucose tolerance.
Cardiovascular disorders	Thrombo-embolic disorders: thrombophlebitis and pulmonary embolism.
Skin and mucosa disorders	Urticaria, pruritus, rash, acne, hirsutism, alopecia
Immune system disorders	Hypersensitivity reactions (e.g. anaphylaxis and anaphylactoid reactions, angioedema).
Musculoskeletal disorders	Asthenia, cramp in the legs, back pain, arthralgia, loss of bone mineral density, reactions at the injection site (pain, residual swelling and cutaneous discoloration)
Miscellaneous	Hyperpyrexia, modification of body weight, oedema/fluid retention, moon face.

In postmarketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients using intramuscular injections of medroxyprogesterone acetate.

4.9 Overdose

Medroxyprogesterone acetate has been very well tolerated. In the case of overdose, nausea and vomiting may occur. Withdrawal bleeding is possible.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Medroxyprogesterone acetate (17-alpha-hydroxyl-6-alpha-methylprogesterone acetate) is a progesterone derivative.

Pharmacotherapeutic group: progestogen

After IM injection, Medroxyprogesterone acetate injectable suspension 150 mg/mL has a long-lasting progestogen action.

Medroxyprogesterone acetate is a progestational agent devoid of androgenic and estrogenic activity.

Medroxyprogesterone acetate injectable suspension 150 mg/mL suppresses the secretion of pituitary gonadotrophins which, in turn, prevents follicular maturation and ovulation during a long period in women of childbearing potential. This action may also account for the ability of

Medroxyprogesterone acetate injectable suspension 150 mg/mL to ameliorate vasomotor symptoms in the menopausal woman. In male patients, adequate doses of Medroxyprogesterone acetate injectable suspension 150 mg/mL suppress the Leydig cell function (i.e. suppress the endogenous testosterone production).

Medroxyprogesterone acetate also induces specific progestational changes in the cervical mucus:

- Prevents ferning
- Increases the viscosity, thus rendering sperm penetration more difficult.

The maturation index in the vaginal epithelium (increase in the intermediate cell count) also changes.

The efficacy of Medroxyprogesterone acetate injectable suspension 150 mg/mL at pharmacological doses in cancer is probably linked with its activity on the hypothalamo-pituitary-gonadal axis and the oestrogen receptors and with the tissular metabolism of steroids.

Like progesterone, medroxyprogesterone acetate is thermogenic.

No suppression of adrenocortical activity has been observed at clinical level at the doses used to inhibit ovulation. However, at very high doses (500 mg or more per day), as used in certain types of cancer, the drug can demonstrate a corticoid-like activity.

Studies on bone mineral density:

Bone mineral density changes in adult women:

In a controlled, clinical study, adult women using injections of medroxyprogesterone acetate (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density decreases of 5-6%, compared to no significant change in bone mineral density in the control group. The decline in bone mineral density was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes were observed in lumbar spine bone mineral density of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively. Mean decreases in bone mineral density of the total hip and femoral neck were similar.

After stopping medroxyprogesterone acetate injections (150 mg IM), there was progressive recovery of bone mineral density toward baseline values during the 2-year post-therapy period. After 2 years without treatment, the bone mineral density deficiency had decreased to

approximately 2.1% in the spine and hip. A longer duration of treatment was associated with a slower rate of bone mineral density recovery(see section **Special warnings and precautions for use** – Loss of bone mineral density).

Bone mineral density changes in adolescent females (12-18 years):

An open-label non-randomised clinical study in adolescent females (12-18 years) using of Medroxyprogesterone acetate injectable suspension (150 mg IM every 3 months for up to 240 weeks [4.6 years]) for contraception also showed a significant decline in bone mineral density from baseline. Among subjects who received ≥ 4 injections/60 week period, the mean decrease in lumbar spine bone mineral density was -2.1% after 240 weeks; mean decreases for the total hip and femoral neck were -6.4% and -5.4% respectively. Post-treatment follow-up showed that lumbar spine bone mineral density recovered to baseline levels approximately 1 year after treatment was discontinued and that hip bone mineral density recovered to baseline levels approximately 3 years after treatment was discontinued. In contrast, unmatched untreated subjects showed mean bone mineral density increases at 240 weeks of 6.4%, 1.7% and 1.9% for lumbar spine, total hip and femoral neck, respectively(see section **Special warnings and precautions for use**– Loss of bone mineral density).

Pharmacokinetic properties

Following intramuscular administration, medroxyprogesterone acetate is slowly released, resulting in low, but persistent blood levels. Time to serum peak is approximately 4 to 20 days following an intramuscular dose. Medroxyprogesterone acetate can still be detected in blood for as long as seven to nine months following intramuscular injection.

Medroxyprogesterone acetate is approximately 90 to 95% protein bound. Its distribution volume is 20 ± 3 litres. Medroxyprogesterone acetate crosses the blood-brain-barrier and is excreted in breast milk.

Numerous metabolites of medroxyprogesterone acetate have been described, although not clearly quantified.

The drug's half life after intramuscular administration is 6 weeks.

Medroxyprogesterone acetate is primarily excreted in the faeces, via biliary secretion. Approximately 44% of the drug is excreted unchanged in urine.

Preclinical safety data

No data held.

6. PHARMACEUTICAL PARTICULARS**6.1 List of Excipients**

Polysorbate 80, polysorbate glycol, methyl paraben 1.37 mg, propyl paraben 0.15 mg, water for injections, sodium chloride, hydrochloric acid and/or sodium hydroxide for the pH adjustment.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze.

6.5 Nature and contents of container

Medroxyprogesterone Acetate Injectable Suspension USP 150 mg/mL: 2 mL/13 mm USP Type I clear tubular glass vials (Fiolax) and 13mm grey bromobutyl rubber stopper (V-35 4405/50/GREY RS SIL-2 Westar®) and 13mm flip off seals white WE-01.

6.6 Special precautions for disposal and other handling

Vial: shake well just before use in order to obtain homogeneous suspension.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF THE MANUFACTURER AND MARKETING AUTHORISATION HOLDER

Mylan Laboratories Limited,

Plot No. – 20 & 21,

Pharmez, Sarkhej – Bavla,

National Highway No. - 8 – A,
Near Village – Matoda, Tal – Sanand, Dist.-
Ahmedabad – 382 213, India.

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08614/07436/NMR/2019

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