SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEPO PROVERA® 150 mg/ml suspension for injection
Medroxyprogesterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Depot-medroxyprogesterone acetate (DMPA) injectable suspension is available in vials as 150 mg/mL

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for intramuscular (IM) injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DEPO-PROVERA is indicated for:

Contraception
Long-term Use
Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO- PROVERA injection long-term (see Section 4.4. Special warnings and precautions for use - Additional Warnings and Precautions, Contraception - Injectable Formulations: Loss of Bone Mineral Density and Section 5.1. Pharmacodynamic properties - Clinical Studies, Bone Mineral Density Studies), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Use in Children
DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12-18 years) (see Section 5.1. Pharmacodynamic properties - Clinical Studies, BMD Changes in Adolescent Females (12-18 years). The safety and effectiveness of DEPO- PROVERA are expected to be the same for postmenarcheal adolescent and adult females.

4.2. Posology and method of administration

The injectable suspension should be shaken well before use.

Contraception

DEPO-PROVERA should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

Intramuscular (IM)

The recommended dose is 150 mg of DEPO-PROVERA injectable suspension every 3 months (12-13 weeks) administered by intramuscular injection in the gluteal or deltoid muscle. The IM suspension is not formulated for subcutaneous injection.

First injection

The initial injection should be given during the first 5 days after the onset of a normal menstrual period; within 5 days postpartum if not breast-feeding; or, if exclusively breast-feeding, at or after 6 weeks postpartum.

Second and subsequent injections

If the time interval between IM injections is greater than 13 weeks, pregnancy should be ruled out before administering the next IM injection.

Switching from other methods of contraception

When switching from other contraceptive methods, DEPO-PROVERA 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 DEPO-PROVERA 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 (MPA). However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolized in patients with severe liver insufficiency (see Section 4.3. Contraindications).

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 the following conditions:

- Known suspected pregnancy
- Undiagnosed vaginal bleeding
- Severe liver dysfunction
- Known hypersensitivity to MPA or any component of the drug

Additional Contraindication(s) for Specific Use

Contraception: Known or suspected malignancy of the breast

4.4. Special warnings and precautions for use

General

- Unexpected vaginal bleeding during therapy with MPA should be investigated.
- MPA 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.
- Patients with a history of treatment for clinical depression should be carefully monitored while receiving MPA therapy.

- Some patients receiving MPA may exhibit a decreased glucose tolerance. Diabetic patients should be carefully observed while receiving such therapy.
- The pathologist (laboratory) should be informed of the patient's use of MPA if endometrial or endocervical tissue is submitted for examination.
- The physician/laboratory should be informed that use of MPA may decrease the levels of the following endocrine biomarkers:

a. Plasma/urinary steroids (e.g., cortisol, estrogen, pregnanediol, progesterone, testosterone)

b. Plasma/urinary gonadotrophins (e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

c. Sex hormone-binding-globulin

- 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.
- MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders however, MPA is not recommended in any patient with a history of venous thromboembolism (VTE). Discontinuation of MPA is recommended in patients who develop VTE while undergoing therapy with MPA.
- Meningiomas have been reported following long term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Additional Warnings and Precautions Contraception - Injectable Formulations Loss of Bone Mineral Density (BMD)

Use of DMPA injection 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. 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 DMPA injection 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 DMPA injection is discontinued and ovarian estrogen production increases (see Section 5.1 – Pharmacodynamic Properties, Clinical Studies, BMD Studies). 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 – Pharmacodynamic Properties, Clinical Studies, BMD Studies - BMD recovery post-treatment in adolescent women).

In adults, BMD was observed for a period of 2 years after DMPA 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 – Pharmacodynamic Properties, Clinical Studies, BMD Studies - BMD Changes in Adult Women). 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 – Pharmacodynamic Properties, Clinical Studies, BMD Studies - Relationship of fracture incidence to use of DMPA injectable (150 mg IM) or non-use by women of reproductive age).

Other birth control methods should be considered in the risk/benefit analysis for the use of DMPA injection 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 (BMI) or eating disorder, e.g., anorexia nervosa or bulimia
- Metabolic bone disease
- Strong family history of osteoporosis

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

Contraception

- Most women using DMPA injectable suspension experience disruption of menstrual bleeding patterns (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding). As women continue using DMPA injectable suspension, fewer experience irregular bleeding and more experience amenorrhoea.
- Long-term case-controlled surveillance of users of DMPA injectable suspension found slight or no increased overall risk of breast cancer and no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer.
- DMPA IM injectable suspension has a prolonged contraceptive effect. The median time to conception following the last injection, for those who do conceive, is 10 months, with a range of 4 to 31 months, and is unrelated to the duration of use.

There was a tendency for women to gain weight while on therapy with DMPA.

- If jaundice develops, consideration should be given to not readminister the drug.

Sexually Transmitted Infections

Women should be counseled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (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.

Breast Cancer

The use of combined oral estrogen/progestin by postmenopausal women has been reported to increase the risk of breast cancer. Results from a randomized placebo-controlled trial, the WHI trial, and epidemiological studies (see Section 5.1 - Pharmacodynamic properties, Clinical Studies) have reported an increased risk of breast cancer in women taking estrogen/progestin combinations for HT for several years. In the WHI conjugated equine estrogens (CEE) plus MPA trial and observational studies, the excess risk increased with duration of use. The use of estrogen plus progestin has also been reported to result in an increase in abnormal mammograms requiring further evaluation.

In several epidemiologic studies no overall increased risk for breast cancer was found among users of injectable depot progestogens in comparison to non-users. However, an increased relative risk (e.g. 2.0 in one study) was found for women who currently used injectable depot 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 current users is due to increased surveillance among current users, the biological effects of injectable progestogens, or a combination of reasons.

Cardiovascular Disorders

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. Several randomized, prospective trials on the long-term effects of a combined estrogen/progestin regimen in postmenopausal women have reported an increased risk of cardiovascular events such as myocardial infarction, coronary heart disease, stroke, and venous thromboembolism.

- Coronary Artery Disease

There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated estrogen and medroxyprogesterone acetate (MPA). Two large clinical trials [WHI CEE/MPA and Heart and Estrogen/progestin Replacement Study (HERS) (see Section 5.1 - Pharmacodynamic properties, Clinical Studies) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit.

In the WHI CEE/MPA trial, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CEE/MPA compared to women receiving placebo (37 vs. 30 per 10,000 person years). The increase in VTE risk was observed in year one and persisted over the observation period

- Stroke

In the WHI CEE/MPA trial, an increased risk of stroke was observed in women receiving CEE/MPA compared to women receiving placebo (29 vs. 21 per 10,000 person-years). The increase in risk was observed in year one and persisted over the observation period

- Venous thromboembolism / Pulmonary embolism

HT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. In the WHI CEE/MPA trial, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism was observed in women receiving CEE/MPA compared to women receiving placebo. The increase in risk was observed in year one and persisted over the observation period (see Section 4.4-Special warnings and precautions for use).

Dementia

The Women's Health Initiative Memory Study (WHIMS) (see Section 5.1 Pharmacodynamic Properties - Clinical Studies), an ancillary study of WHI, CEE/MPA reported an increased risk of probable dementia in postmenopausal women 65 years of age or older. In addition, CEE/MPA therapy did not prevent mild cognitive impairment (MCI) in these women. Use of hormone therapy (HT) to prevent dementia or MCI in women 65 years or older is not recommended

Ovarian Cancer

Current use of estrogen only or estrogen plus progestin products in post-menopausal women for five or more years, has been associated with an

increased risk of ovarian cancer in some epidemiological studies. Past users of estrogen only or estrogen plus progestin products were at no increased risk for ovarian cancer. Other studies did not show a significant association. The WHI CEE/MPA trial reported that estrogen plus progestin increased the risk of ovarian cancer, but this risk was not statistically significant. In one study, women who use HRT are at increased risk of fatal ovarian cancer.

History and Physical Exam Recommendation

A complete medical and family history should be taken before the initiation of any hormone therapy. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including cervical cytology.

4.5. Interaction with other medicinal products and other forms of interaction

Medroxyprogesterone acetate (MPA) is metabolized in-vitro primarily by hydroxylation via the CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

4.6. Fertility, pregnancy and lactation

Pregnancy and lactation

MPA is contraindicated in women who are pregnant.

Some reports suggest under certain circumstances, an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in fetuses.

Infants from unintentional pregnancies that occur 1 to 2 months after injection of DMPA injectable suspension may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. The attributable risk is low because pregnancies while on DMPA are uncommon. There is no definitive information for the other formulations of MPA, (see Section 5.2 Pharmacokinetic properties - Distribution).

If the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Breast-feeding

MPA and its metabolites are excreted in breast milk. There is no evidence to suggest that this presents any hazard to the nursing child (see Section 5.2, Pharmacokinetic properties, Distribution).

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

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylactic reaction, anaphylactoid reaction, angioedema, drug hypersensitivity
Endocrine disorders	Prolonged anovulation

Psychiatric disorders	Depression, insomnia, nervousness, anorgasmia, libido decreased
Nervous system disorders	Seizure, dizziness, headache, somnolence
Vascular disorders	Embolism and thrombosis, hot flush
Gastrointestinal disorders	Abdominal pain, abdominal discomfort, nausea, abdominal distension
Hepatobiliary disorders	Jaundice, liver disorder
Skin and subcutaneous tissue disorders	Alopecia, acne, hirsutism, urticaria, lipodystrophy acquired*, pruritus, rash
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, muscle spasms
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, pelvic pain, vaginitis, amenorrhoea, breast pain, vaginal discharge, breast tenderness
General disorders and administration site conditions	Fluid retention, pyrexia, fatigue, asthenia, injection-site reaction*, injection site persistent atrophy/indentation/dimpling*, injection site nodule/lump*, injection site pain/tenderness*
Investigations	Bone density decreased, glucose tolerance decreased, weight increased, weight decreased
*ADR identified post-marketing	

Additional Adverse Events Reported During Post-Marketing Experience:

In post-marketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients taking DMPA IM.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9. Overdose

Overdose treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Mechanism of action

MPA is a synthetic progestin (structurally related to the endogenous hormone progesterone) which has been demonstrated to possess several pharmacologic actions on the endocrine system:

- Inhibition of pituitary gonadotropins (FSH and LH);
- Decrease of ACTH and hydrocortisone blood levels;

- Decrease of circulating testosterone;
- Decrease of circulating estrogen levels (as the result of both FSH inhibition and enzymatic induction of hepatic reductase, resulting in increased clearance of testosterone and consequent decreased conversion of androgens to estrogens).

All of these actions result in a number of pharmacological effects, as described below.

Contraception

DEPO-PROVERA when administered parenterally at the recommended dose to women, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and causes thickening of cervical mucus which inhibits sperm entry into the uterus.

Clinical studies

BMD Studies

BMD Changes in Adult Women

In a non-randomized controlled clinical study comparing adult women using DMPA contraceptive injection (150 mg IM) for up to 5 years to women who elected to use no hormonal contraception, 42 DMPA users completed 5 years of treatment and provided at least 1 follow-up BMD measurement after stopping DMPA. Among DMPA users, BMD declined during the first 2 years of use, with little declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% 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 DMPA injection (150 mg IM)

After 5 years of treatment with DMPA injection (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 DMPA injections, 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 (12-18 years)

The effect of DMPA injectable (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 DMPA; 114 of the 159 participants used DMPA 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 DMPA 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 DMPA 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 DMPA 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 DMPA injection and provided at least 1 follow-up BMD measurement after stopping DMPA use, with DMPA treatment for up to 240 weeks (equivalent to 20 DMPA injections) and post-treatment follow-up extending for up to 240 weeks after the final DMPA injection. The median number of injections received during the treatment phase was 9. At the time of the final DMPA 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 DMPA 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. Special warnings and precautions for use - Additional Warnings and Precautions, Contraception - Injectable Formulations: Loss of Bone Mineral Density (BMD).
Relationship of fracture incidence to use of DMPA injectable (150 mg IM) or non-use by women of reproductive age
A retrospective cohort study to assess the association between DMPA injection 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 DMPA use started and also between DMPA users and women who used other contraceptives but had no recorded use of DMPA. Among women using DMPA, use of DMPA was not associated with an increase in fracture risk (incident rate ratio = 1.01, 95% CI 0.92-1.11, comparing the study follow-up period with up to 2 years of observation prior to DMPA use). However, DMPA 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 DMPA users compared to non-users (IRR = 0.95, 95% CI 0.74-1.23), nor was there any evidence that longer use of DMPA (2 years or more) confers greater risk for fracture compared to less than 2 years of use.

These data demonstrate that DMPA users have an inherently different fracture risk profile to non-users for reasons not related to DMPA use.
Maximum follow-up in this study was 15 years, therefore, possible effects of DMPA that might extend beyond 15 years of follow-up cannot be determined.

Women's Health Initiative Study
The WHI CEE (0.625mg)/MPA (2.5mg) trial enrolled 16,608 postmenopausal women aged 50- 79 years with intact uteri at baseline, to assess the risks and benefits of the combined therapy compared with placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with

invasive breast cancer as the primary adverse outcome studied. The study was stopped early after an average follow-up of 5.2 years (planned duration 8.5 years) because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index" (see Section 4.4. Special warnings and precautions for use, Breast Cancer).
The combination CEE/MPA therapy reported a significant decrease in osteoporotic (23%) and total (24%) fractures.

Million Women Study
The MWS was a prospective cohort study enrolling 1,084,110 women in the UK aged 50-64 years of whom 828,923 with defined time since menopause were included in the main analyses of risk of breast cancer in relation to HT. Overall, 50% of the study population had used HT at some point. Most current users of HT at baseline reported using preparations containing estrogen only (41%) or estrogen-progestin combinations (50%). The average duration of follow-up was 2.6 years for analyses of cancer incidence and 4.1 years for analyses of mortality (see Section 4.4 Special warnings and precautions for use, Breast Cancer).

Heart and Estrogen/progestin Replacement Studies
HERS and HERS II studies were two randomized, prospective secondary prevention trials on the long-term effects of oral continuous combined CEE/MPA (0.625 mg CEE plus 2.5mg MPA) regimen in postmenopausal women with CHD (see Section 4.4. Special warnings and precautions for use - Cardiovascular disorders). 2, 763 postmenopausal women with a mean age of 66.7 years and with intact uteri were enrolled in this study. The average duration of follow-up was 4.1 years for HERS and 2.7 additional years (for a total of 6.8 years) for HERS II (see Section 4.4. Special warnings and precautions for use - Cardiovascular Disorders).

Women's Health Initiative Memory Study
The WHIMS, a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women age 65 to 79 years to evaluate the effects of CEE/MPA (0.625 mg CEE plus 2.5 mg MPA) or CEE-alone (0.625 mg) on the incidence of probable dementia compared with placebo. The average duration of follow-up was 4.05 years for the CEE/MPA (see Section 4.4. Special warnings and precautions for use - Dementia).

5.2. Pharmacokinetic properties

Absorption

Following intramuscular administration, MPA is slowly released, resulting in low, but persistent levels in the circulation. Immediately after intramuscular injection of 150mg/ml MPA, plasma levels were 1.7 ± 0.3 nmol/L. Two weeks later, levels were 6.8 ± 0.8 nmol/L. Mean time to peak is approximately 4 to 20 days following an intramuscular dose. Serum medroxyprogesterone acetate levels gradually decline and remain relatively constant at about 1 ng/mL for 2-3 months. Circulating levels can be detected for as long as 7 to 9 months following an intramuscular injection.

Distribution

MPA is approximately 90 to 95 % protein bound. Volume of distribution is reported as 20 + 3 liters. Medroxyprogesterone acetate crosses the blood-brain-barrier, and the placental barrier (see Section 4.6. Pregnancy and lactation). Low levels of medroxyprogesterone acetate have been detected in breast milk of lactating women (see Section 4.6 – Pregnancy and lactation) administered 150 mg of medroxyprogesterone acetate by the IM route.

Metabolism

MPA is metabolized in the liver.

Elimination

The elimination half-life following single intramuscular injection is about weeks. Medroxyprogesterone acetate is primarily excreted in the feces, via biliary secretion. Approximately 30% of an intramuscular dose is secreted in the urine after 4 days.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term intramuscular administration of medroxyprogesterone acetate (DMPA) has been shown to produce mammary tumors in beagle dogs. Medroxyprogesterone acetate was not mutagenic in a battery of in vitro or in vivo genetic toxicity assays. Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Macrogol 3350,
polysorbate 80,
sodium chloride,
methyl parahydroxybenzoate (E218),
propyl parahydroxybenzoate (E216),
water for injections,
hydrochloric acid and/or sodium hydroxide for the pH adjustment.

6.2. Incompatibilities

The injectable forms should not be mixed with any other agent.

6.3. Shelf life

Do not use DEPO-PROVERA after the expiry date which is stated on the Carton/Vial label after EXP:. The expiry date is mentioned on the package after the letters EXP. (EXP. = expiry date).

48 months

6.4. Special precautions for storage

Store at a temperature below 30°C.

6.5. Nature and contents of container

Sterile aqueous suspension for intramuscular injection. Presentations:

DEPO-PROVERA 150 mg suspension for injection:
- 1 ml vial

DEPO-PROVERA 150 mg/ml suspension for injection:
- 25 ml vial

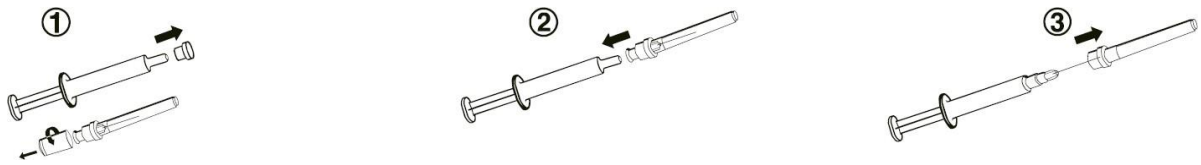
Not all presentations may be marketed.

6.6. Special precautions for disposal and other handling

Vial: shake well just before use in order to obtain homogeneous suspension.
Pre-filled syringe: shake well just before use in order to obtain homogeneous suspension.

1. Remove the protective cap.
2. Fit the needle to the syringe.
3. Remove the protective sheath from the needle.

The syringe is ready to use.



After use, the syringe cannot be reused and must be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Pfizer Laboratories Limited Kenya,
1st Floor Vienna Court, West Wing,
State House Crescent Road, Nairobi, Kenya.

Manufacturer
Pfizer Manufacturing Belgium NV
Address: , Rijksweg 12, 2870 Puurs-Sint-Amands

8. Marketing authorization number(s)

782

9. Date of First Authorization

19th Jan 2012

10. Date of revision of text

March 2024