DEPO-PROVERA™
Sterile Aqueous Suspension 50 mg/mL

1. NAME OF THE MEDICINAL PRODUCT

Depo-Provera Sterile Aqueous Suspension 50 mg/mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Depo-Provera Sterile Aqueous Suspension 50 mg/mL: Each mL of injectable suspension contains 50 mg of medroxyprogesterone acetate.

For excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Suspension for intramuscular (IM) injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Medroxyprogesterone acetate (MPA) injectable suspension is indicated for:

Contraception
Contraception (ovulation suppression).

Gynecology
Treatment of endometriosis.
Treatment of menopausal vasomotor symptoms.

Oncology
Adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma.

Treatment of hormonally-dependent, recurrent breast cancer in post-menopausal women.

Long-term Use
Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA injection long-term (see **Section 4.4 Special warnings and precautions for use - Additional Warnings and Precautions for Specific Use or Formulation, *Contraception/Endometriosis - Injectable Formulations*, Loss of Bone Mineral Density (BMD)** and **Section 5.1 Pharmacodynamic properties - *Clinical Studies*, BMD 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
MPA IM 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 MPA IM are expected to be the same for post-menarcheal adolescent and adult females.

4.2 Posology and method of administration

Injectable suspensions should be shaken well before use.

Contraception
Contraception (Ovulation Suppression)
MPA intramuscular injectable suspension 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 MPA injectable suspension every 12-13 weeks (3 months) administered by intramuscular injection in the gluteal or deltoid muscle.

First injection
The initial IM 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.

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, (MPA IM) should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods.

Gynecology
Use of combined estrogen/progestin therapy in post-menopausal women should be limited to the lowest effective dose and shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically evaluated (see **Section 4.4 Special warnings and precautions for use**).

Periodic check-ups are recommended of a frequency and nature adapted to the individual woman (see **Section 4.4 Special warnings and precautions for use**).

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestin in a woman without an intact uterus.

Endometriosis
Injectable MPA given intramuscularly 50 mg weekly or 100 mg every 2 weeks for at least 6 months.

Menopausal Vasomotor Symptoms
Injectable MPA given intramuscularly 150 mg every 12 weeks.

Oncology
Endometrial and Renal Carcinoma
Injectable MPA 400 mg to 1,000 mg intramuscularly per week is recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilized, it may be possible to maintain improvement with as little as 400 mg per month.

Breast Cancer
Injectable MPA 500 mg/day intramuscularly for 28 days. The patient should then be placed on a maintenance schedule of 500 mg twice weekly as long as she responds to treatment.

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 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

MPA is contraindicated in patients with the following conditions:
- Known or suspected pregnancy
- Undiagnosed vaginal bleeding
- Severe liver dysfunction
- Known sensitivity to MPA or any component of the drug

Additional Contraindication(s) for Specific Use

Contraception/Gynecology: 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 gonadotropins (e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH))

    c. Sex-hormone-binding-globulin

- Medication should not be re-administered, 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.

Additional Warnings and Precautions for Specific Use or Formulation

Contraception/Endometriosis - Injectable Formulations

Loss of Bone Mineral Density (BMD)

Use of MPA 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 MPA injection during adolescence and early adulthood will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be at least partially reversible after MPA 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 adolescents).

In adults, BMD was observed for a period of 2 years after MPA injection was

discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine. A longer duration of treatment was associated with a slower rate of BMD recovery (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 MPA injectable (150 mg IM) or non-use by women of reproductive age).

BMD Changes in Adult Women after Six Months of Treatment for Endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of MPA-SC treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months.

The proportion of patients with a decrease of 5% or more in BMD was statistically significantly greater in the leuprolide group compared with MPA-SC at each time point (Table 1).

Table 1. Proportion of Patients with a Decrease of 5% or More from Baseline after 6 Months on Therapy with MPA-SC or Leuprolide and 6 Months after Stopping Therapy (Studies 268 and 270 Combined)

BMD Parameter	MPA-SC n/N* (%)	Leuprolide n/N* (%)	p-value**
End of Treatment (6 Months of Therapy)			
Spine	12/208 (5.8%)	85/229 (37.1%)	<0.001
Total Hip	1/207 (0.5%)	25/227 (11.0%)	<0.001
At 12 Month Visit (6 Months Off-Therapy)			
Spine	8/166 (4.8%)	32/178 (18.0%)	<0.001
Total Hip	3/166 (1.8%)	25/178 (14.0%)	<0.001

* n=number of patients with a decrease in BMD ≥5%; N=total observations.
** Chi-square.

Other birth control methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA 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 MPA injectable suspension experience disruption of menstrual bleeding patterns (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding). As women continue using MPA injectable suspension, fewer experience irregular bleeding and more experience amenorrhoea.

- Long-term case-controlled surveillance of users of MPA 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.

- MPA 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 MPA.

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

Sexually Transmitted Infections

Women should be counseled that MPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, MPA 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.

Gynecology

Treatment of Menopausal Vasomotor Symptoms/Opposition of Endometrial Effects of Estrogen in Menopausal Women Being treated with Estrogen (Hormone Therapy) - All Formulations:

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of Hormone Therapy (HT) were not studied in the Women's Health Initiative (WHI) trial (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies*, Women's Health Initiative Study**) and, in the absence of comparable data, these risks should be assumed to be similar.

Breast Cancer

The use of combined oral estrogen/progestin by post-menopausal 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 (see **Section 4.2 Posology and method of administration**). The use of estrogen plus progestin has 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.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed against the known benefits.

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 (see **Section 4.2 Posology and method of administration**) of a combined estrogen/progestin regimen in post-menopausal 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 non-fatal 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 (see **Section 4.2 Posology and method of administration**).

- 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 (see **Section 4.2 Posology and method of administration**).

- 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 developing probable dementia and mild cognitive impairment (MCI) in post-menopausal 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.

Gynecology-injectable Formulations

- Prolonged anovulation with amenorrhoea and/or erratic menstrual patterns may follow the administration of either a single or multiple injectable dose of MPA.

Oncology

- MPA may produce Cushingoid symptoms.

- Some patients receiving MPA may exhibit suppressed adrenal function. MPA may decrease ACTH and hydrocortisone blood levels.

- The physician/laboratory should be informed that in addition to the endocrine biomarkers listed in **Section 4.4 Special warnings and precautions for use**, the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of adrenal cortex to respond to ACTH should be demonstrated before metyrapone is administered.

Oncology-injectable Formulations

- Prolonged anovulation with amenorrhoea and/or erratic menstrual patterns may follow the administration of either a single or multiple injectable dose of MPA.

High Dose Parenteral Formulations (e.g., oncology use in pre-menopausal women)

Decrease in Bone Mineral Density

There are no studies on the bone mineral density (BMD) effects of high doses of parenteral MPA (e.g., for oncology use). However, two clinical studies of adult women of childbearing potential and of adolescent females given Depo-Provera 150 mg IM every three months for contraception, demonstrated significant decreases in BMD (see above - **Loss of Bone Mineral Density**). Decreases in serum estrogen due to Depo-Provera may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. It is recommended that all patients have adequate calcium and vitamin D intake. An evaluation of BMD may be appropriate in some patients who use MPA long-term.

4.5 Interactions with other medicinal and other forms of interaction

Aminoglutethimide administered concomitantly with high doses of MPA may significantly depress the serum concentrations of medroxyprogesterone acetate. Users of high-dose MPA should be warned of the possibility of decreased efficacy with the use of aminoglutethimide.

Medroxyprogesterone acetate (MPA) is metabolized *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur. Combined use of MPA with CYP3A4 inhibitors or inducers may result in compromised efficacy due to decreased systemic levels of MPA with co-administration of inducers or increased systemic levels of MPA with co-administration of inhibitors.

4.6 Pregnancy and lactation

Pregnancy

MPA is contraindicated in women who are pregnant.

Some reports suggest 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 MPA 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 MPA 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.

Lactation

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

Contraception

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 4200 women who received MPA for contraception for up to 7 years. Those most frequently (>5%) reported adverse drug reactions were weight increased (69%), weight decreased (25%), headache (16%), nervousness (11%), abdominal pain or discomfort (11%), dizziness (6%), and decrease in libido (6%).

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Immune system disorders			Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Endocrine disorders				Prolonged anovulation
Psychiatric disorders	Nervousness	Depression, Libido decreased	Insomnia	Anorgasmia
Nervous system disorders	Headache	Dizziness	Seizure, Somnolence	
Vascular disorders			Hot flush	Embolism and thrombosis
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort	Nausea, Abdominal distension		
Hepatobiliary disorders			Liver disorder	Jaundice

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Skin and subcutaneous tissue disorders		Alopecia, Acne, Rash	Hirsutism, Urticaria, Pruritus	Lipodystrophy acquired*
Musculoskeletal and connective tissue disorders		Back pain		Arthralgia, Muscle spasms
Reproductive system and breast disorders		Vaginal discharge, Breast tenderness	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Galactorrhoea Pelvic pain	Vaginitis, Amenorrhoea, Breast pain
General disorders and administration site conditions		Fluid retention, Asthenia		Pyrexia, Fatigue, Injection site reaction*, Injection site persistent atrophy/indentation/ dimpling*, Injection site nodule/lump*, Injection site pain/tenderness*
Investigations	Weight increased, Weight decreased			Bone density decreased, Glucose tolerance decreased
*ADR identified post-marketing				

Gynecology

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from Phase 3 clinical studies that evaluated efficacy and safety of MPA in gynecology. Those most frequently (>5%) reported adverse drug reactions were dysfunctional uterine bleeding (19%), headache (12%), and nausea (10%):

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Not Known (cannot be estimated from available data)
Immune system disorders		Drug hypersensitivity		Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Endocrine disorders				Prolonged anovulation
Psychiatric disorders		Depression, Insomnia, Nervousness		
Nervous system disorders	Headache	Dizziness		Somnolence
Vascular disorders				Embolism and thrombosis
Gastrointestinal disorders	Nausea			
Hepatobiliary disorders				Jaundice, Jaundice cholestatic
Skin and subcutaneous tissue disorders		Alopecia, Acne, Urticaria, Pruritus	Hirsutism	Lipodystrophy acquired*, Rash
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)	Cervical discharge, Breast pain, Breast tenderness	Galactorrhoea	Amenorrhoea, Uterine cervical erosion
General disorders and administration site conditions		Pyrexia, Fatigue, Injection site reaction*, Injection site persistent atrophy/indentation/ dimpling*	Oedema, Fluid retention, Injection site nodule/lump*, Injection site pain/tenderness*	
Investigations		Weight increased		Glucose tolerance decreased, Weight decreased
*ADR identified post-marketing				

Oncology

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from 1337 patients who received MPA in 4 pivotal studies that evaluated efficacy and safety of MPA for oncology indications.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to < 1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Frequency Not Known (cannot be estimated from the available data)
Immune system disorders			Angioedema	Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction
Endocrine disorders			Corticoid-like effects		Prolonged anovulation
Metabolism and nutritional disorders		Weight fluctuation, Increased appetite	Diabetes mellitus exacerbated, Hypercalcaemia		
Psychiatric disorders		Insomnia	Depression, Euphoria, Changes in libido	Nervousness	Confusion
Nervous system disorders		Headache, Dizziness, Tremors		Cerebral infarction, Somnolence	Loss of concentration, Adrenergic-like effects
Eye disorders					Retinal embolism and thrombosis, Cataract diabetic, Visual impairment
Cardiac disorders			Cardiac failure congestive	Myocardial infarction	Tachycardia, Palpitations
Vascular disorders			Thrombophlebitis	Embolism and thrombosis	
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism		
Gastrointestinal disorders		Vomiting, Constipation, Nausea	Diarrhoea, Dry mouth		
Hepatobiliary disorders				Jaundice	
Skin and subcutaneous tissue disorders		Hyperhidrosis	Acne, Hirsutism	Alopecia, Rash	Lipodystrophy acquired*, Urticaria, Pruritus
Musculoskeletal and connective tissue disorders			Muscle spasms		
Renal and urinary system disorders					Glycosuria
Reproductive system and breast disorders		Erectile dysfunction	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Breast pain		Amenorrhoea, Uterine cervical erosions, Cervical discharge, Galactorrhoea

System Organ Class	Very Common ≥1/10	Common ≥1/100 to < 1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Frequency Not Known (cannot be estimated from the available data)
General disorders and administration site conditions		Oedema/fluid retention, Fatigue, Injection site reaction*	Injection site pain/tenderness*	Malaise, Pyrexia	Injection site persistent atrophy/indentation/dimpling*, Injection site nodule/lump*
Investigations				Glucose tolerance decreased, Blood pressure increased	Liver function test abnormal, White blood cell count increased, Platelet count increased
*ADR identified post-marketing					

Additional Adverse Events Reported During Post-Marketing Experience:

Intramuscular Formulations
In post-marketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients taking MPA IM. There were also cases where a role of IM medroxyprogesterone in the development of injection site atrophy, necrosis, lipoatrophy, skin atrophy, skin necrosis and injection site ulcer cannot be ruled out.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated.

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

MPA, 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.

Gynecology

Medroxyprogesterone acetate (MPA), administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parenterally administered MPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

Oncology

MPA demonstrates antitumor activity. When MPA is given to patients at high doses (either by the oral route or by IM injection) it is effective in the palliative treatment of hormone-response, malignant neoplasms.

Clinical Studies

BMD Studies

BMD Changes in Adult Women

In a non-randomized controlled clinical study comparing adult women using MPA contraceptive injection (150 mg IM) for up to 5 years to women who elected to use no hormonal contraception, 42 MPA users completed 5 years of treatment and provided at least 1 follow-up BMD measurement after stopping MPA. Among MPA 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. Spine and hip mean BMD decreases of 5% to 6% among MPA users compared to no significant changes in BMD observed 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 MPA injection (150 mg IM).

After 5 years of treatment with MPA 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 MPA 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 MPA 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 MPA; 114 of the 159 participants used MPA 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 MPA 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 MPA 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 MPA 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 MPA injection and provided at least 1 follow-up BMD measurement after stopping MPA use, with MPA treatment for up to 240 weeks (equivalent to 20 MPA injections) and post-treatment follow-up extending for up to 240 weeks after the final MPA injection. The median number of injections received during the treatment phase was 9. At the time of the final MPA 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 MPA 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 for Specific Use or Formulation, *Contraception/Endometriosis – Injectable Formulations:* Loss of Bone Mineral Density (BMD)**.

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

A retrospective cohort study to assess the association between MPA 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 MPA use started and also between MPA users and women who used other contraceptives but had no recorded use of MPA. Among women using MPA, use of MPA 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 MPA use). However, MPA 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 MPA users compared to non-users (IRR = 0.95, 95% CI 0.74-1.23), nor was there any evidence that longer use of MPA (2 years or more) confers greater risk for fracture compared to less than 2 years of use.

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

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

Women's Health Initiative Study

The WHI CEE (0.625 mg)/MPA (2.5 mg) trial enrolled 16,608 post-menopausal 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) (non-fatal 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 2.5 mg MPA) regimen in post-menopausal women with CHD (see **Section 4.4 Special warnings and precautions for use - Cardiovascular Disorders**). 2,763

post-menopausal 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 post-menopausal 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 Pharmacokinetics properties

Absorption

Following intramuscular administration, MPA is slowly released, resulting in low, but persistent levels in the circulation. Immediately after intramuscular injection of 150 mg/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 6 weeks. Medroxyprogesterone acetate is primarily excreted in the feces, via biliary secretion. Approximately 30% of 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 (MPA) has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of oral MPA to rats and mice. 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

Polysorbate 80
Methylparaben
Propylparaben
Polyethylene glycol 3350
Sodium chloride
Water for Injection.

6.2 Incompatibilities

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

6.3 Shelf-life

Please refer to EXP date on outer carton.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze. Store vial upright.

6.5 Nature and contents of container

Vial

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal should be observed. Vials and used syringes with attached needle are considered as biohazardous waste and should be discarded in puncture-resistant containers.

7. PRODUCT OWNER

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