PFIZER
DEPO-PROVERA®
Medroxyprogesterone acetate

1. NAME OF THE MEDICINAL PRODUCT

DEPO-PROVERA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Depot-medroxyprogesterone acetate (DMPA) injectable suspension is available as 150 mg/3 mL vial.

3. PHARMACEUTICAL FORM

Suspension for intramuscular (IM) injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Depot-Medroxyprogesterone acetate (DMPA) 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 DMPA injection long-term (see **Sections 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 **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.

4.2 Posology and Method of Administration

Injectable suspensions should be shaken well before use.

Contraception

Contraception (Ovulation Suppression)
DMPA intramuscular (IM) 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 DMPA injectable suspension every 3 months administered by intramuscular injection in the gluteal or deltoid muscle. The IM suspension is not formulated for subcutaneous injection.

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 postpartum if not breast-feeding; or, if exclusively breast-feeding, at or after 6 weeks postpartum.

Second and subsequent injection

These should be given at 12 week intervals, however, as long as the injection is given no later than five days after this time, no additional contraceptive measures (e.g. barrier) are required. (N.B. For partners of men undergoing vasectomy, a second injection of 150 mg I.M. 12 weeks after the first may be necessary in a small proportion of patients where the partner's sperm count has not fallen to zero). If the interval from the preceding injection is greater than 89 days (12 weeks and 5 days) for any reason, then pregnancy should be excluded before the next injection is given and the patient should use additional contraceptive measures (e.g., barrier) for 14 days after this subsequent injection.

Switching from other methods of contraception

When switching from other contraceptive methods, (DMPA IM) should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods (e.g., patients switching from oral contraceptives should have their first injection of DMPA within 7 days after taking their last active pill).

Use in Children

DMPA 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)*). Other than concerns about loss of BMD, the safety and effectiveness of DMPA IM are expected to be the same for postmenarcheal adolescent and adult females.

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 with a frequency and nature adapted to the individual woman (see **Section 4.4. Special Warnings and Precautions for Use**).

Endometriosis

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

Menopausal Vasomotor Symptoms

Injectable DMPA given intramuscularly 150 mg every 12 weeks.

Oncology

Recurrent and/or Metastatic Endometrial or Renal Cancer
Injectable DMPA 400 to 1000 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.

Treatment of hormonally-dependent, recurrent breast cancer in post-menopausal women
Injectable DMPA initial dose 500 mg intramuscularly per day 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

The effect of hepatic disease on the pharmacokinetics of Depo-Provera is unknown. As Depo-Provera largely undergoes hepatic elimination it may be poorly metabolised in patients with severe liver insufficiency (see **Section 4.3. Contraindications**).

Renal Insufficiency

The effect of renal disease on the pharmacokinetics of Depo-Provera is unknown. No dosage adjustment should be necessary in women with renal insufficiency, since Depo-Provera is almost exclusively eliminated by hepatic metabolism.

4.3 Contraindications

MPA is contraindicated in patients with the following conditions:
- Known or suspected pregnancy

- Undiagnosed vaginal bleeding
- Severe liver dysfunction
- Known hypersensitivity to MPA or any component of the drug.
- Patient with meningioma or history of meningioma (for non-oncological indications)

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 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.
- Cases of meningioma (single and multiple) have been reported in patients treated with medroxyprogesterone acetate for a prolonged time (several years). Patients treated with medroxyprogesterone acetate should be monitored for signs and symptoms of meningioma in accordance with clinical practice. In some cases, shrinkage of meningioma was observed after treatment discontinuation of depot medroxyprogesterone acetate. If a patient treated for a non-oncological indication is diagnosed with meningioma, medroxyprogesterone acetate must be stopped, as a precautionary measure. If a patient treated for an oncological indication is diagnosed with meningioma, the need for further treatment with medroxyprogesterone acetate should be carefully considered on a case-by-case basis taking into account individual benefits and risks.

Additional Warnings and Precautions for Specific Use or Formulation

Contraception/Endometriosis - 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 or endometrial treatments 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

See below.

Gynecology

Treatment of Menopausal Vasomotor Symptoms/Opposition of Endometrial Effects of Estrogen in Menopausal Women Being Treated with Estrogen (Menopausal Hormone Therapy):

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of Menopausal Hormone Therapy (MHT) 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 MHT 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 also been reported to result in an increase in abnormal mammograms requiring further evaluation.

A large meta-analysis of observational studies reported that when estrogen plus progestin therapy was taken for more than 5 years, the increased risk of breast cancer may persist for 10 years or more after discontinuation of treatment. The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was

taken for less than 5 years. In current users the increased risk of breast cancer in women taking combined estrogen-progestin for MHT becomes apparent after about 1-4 years.

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 (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 probable dementia 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 menopausal hormone therapy (MHT) to prevent dementia or MCI in women 65 years or older is not recommended.

Ovarian Cancer

Current use of estrogen-alone 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-alone 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 MHT 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.

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

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

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 DMPA (e.g., for oncology use). An evaluation of BMD may be appropriate in some patients who use MPA long-term, (**see above – Loss of Bone Mineral Density**).

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 Pregnancy and Lactation

Pregnancy

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 (see **Section 5.2. Pharmacokinetic Properties, *Intramuscular formulations*** - *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, *Intramuscular formulations*** - *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 - Intramuscular (IM) Formulation:

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 DMPA 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**	**Not Known (cannot be estimated from available data)**
Neoplasms benign, malignant & unspecified					meningioma*
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	
Skin and subcutaneous tissue disorders		Alopecia, Acne, Rash	Hirsutism, Urticaria, Pruritus	Lipodystrophy acquired*	
Musculoskeletal and connective tissue disorders		Back pain		Arthralgia, Muscle spasms	

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	Not Known (cannot be estimated from available data)
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.					

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 DMPA IM.

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 DMPA 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)
Neoplasms benign, malignant & unspecified				meningioma*
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)
Neoplasms benign, malignant & unspecified					meningioma*
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		

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)
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
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					

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

DMPA, 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 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. Parenterally administered DMPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation.

Endometriosis

Suppression of serum estradiol concentrations is likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Oncology

MPA demonstrates antitumor activity. When MPA is given to patients at high doses it is effective in the palliative treatment of hormone-responsive malignant neoplasms.

Clinical Studies

<u>BMD Studies</u>

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 for Specific Use, *Contraception/Endometriosis - 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 (0.625 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 MHT. Overall, 50% of the study population had used MHT at some point. Most current users of MHT at baseline reported using preparations containing estrogen-alone (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).

Observational Studies of Breast Cancer Risk

A large meta-analysis of observational studies generated evidence for the type and timing of MHT on breast cancer risk. After ceasing MHT, some excess risk persisted for more than 10 years; its magnitude depended on the duration of previous use.

It was reported that, when estrogen plus progestin therapy was taken for more than 5 years, the increased risk may persist for 10 years or more after discontinuation of treatment:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen+progestin	≥10 years	5-9 years	1.19 (1.10-1.28)
	≥10 years	≥10 years	1.28 (1.15-1.43)

The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen+progestin	≥10 years	<1 year	1.06 (0.95-1.19)
	≥10 years	1-4 years	1.09 (1.00-1.18)

In current users, the increased risk of breast cancer in women taking combined estrogen-progestin MHT becomes apparent after about 1-4 years:

MHT type	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	<1 year	1.08 (0.86-1.35)
	1-4 years	1.17 (1.10-1.26)
Estrogen+progestin	<1 year	1.20 (1.01-1.43)
	1-4 years	1.60 (1.52-1.69)

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 aged 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).

Contraception and Gynecology
Oncology

Meningioma

Based on results from a French epidemiological case-control study, an association between medroxyprogesterone acetate and meningioma has been observed. This study was based on data from the French national health data system (SNDS – Système National des Données de Santé) and included a population of 18,061 women who had intracranial surgery for meningioma and 90,305 women without meningioma. The exposure to medroxyprogesterone acetate 150 mg/3 mL injectable was compared between women who had intracranial surgery for meningioma and women without meningioma. Analyses showed an excess risk of meningioma with the use of medroxyprogesterone acetate 150 mg/3 mL (9/18,061 (0.05%) v 11/90,305 (0.01%), OR 5.55 (95% CI 2.27–13.56)). This excess risk seems to be driven primarily by prolonged use (≥3 years) of medroxyprogesterone acetate.

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 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 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. 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 the expiry date printed on the packaging components.

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

Glass vial in a cardboard carton. Each carton contains one 3 mL vial.

6.6 Special Precautions for Disposal and Other Handling

None

7. MANUFACTURER

Pfizer Manufacturing Belgium NV
Rijksweg 12,
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Belgium

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