NAME OF THE MEDICINAL PRODUCT

Depo Provera 150 mg/ml (Suspension for IM injection)
Depo-Provera 500 (Suspension for IM injection)

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Injectable suspension

Depot-medroxyprogesterone acetate (DMPA) injectable suspension is available as 150 mg/mL, 500 mg/3.3 mL vials.

2. PHARMACEUTICAL FORM

Injectable: suspension for intramuscular injection.

3. CLINICAL PARTICULARS

3.1. Therapeutic indications

DEPO-PROVERA 150 MG/ML (DMPA injectable suspension IM) is indicated for: Contraception where medically indicated and oral administration is inapplicable

DEPO-PROVERA 500 (DMPA injectable IM suspension) are indicated for: Palliation of inoperable recurrent or metastatic carcinoma of endometrium, breast, ovary and kidney.

Long-Term Use

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DMPA injection long-term (see Section 4.4 Special warnings and precautions for use - Additional Warnings & Precautions for Specific Use or Formulation, Contraception / Endometriosis - 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

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 as for postmenarcheal adolescent and adult females.

3.2. Posology and method of administration

Injectable suspensions should be shaken well before use.
Contraception - Intramuscular (IM)

Depo Provera 150 mg/ml - DMPA intramuscular (IM) suspension should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

The recommended dose is 150 mg of DMPA 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 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 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, 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).

Oncology

Recurrent and/or Metastatic Breast Cancer

- Injectable DMPA initial dose 500 to 1000 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.

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

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.

3.3. 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

Additional Contraindication(s) for Specific Use

Contraception:

Known or suspected malignancy of the breast or genital organs

patients with metabolic bone disease.

patients with active thromboembolic disease and in patients with current or past history of cerebrovascular disease.

Oncology

Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease

3.4. 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., LH and 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 papilledema 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 & Precautions for Specific Use or Formulation

Contraception - Injectable Formulations

Loss of Bone Mineral Density (BMD)

Use of Depo-Provera reduces serum oestrogen levels and is associated with significant loss of BMD due to the known effect of oestrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use; however BMD appears to increase after Depo-Provera is discontinued and ovarian oestrogen production increases. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of Depo-Provera by younger women will reduce peak bone mass and increase the risk for fracture in later life.

A study to assess the BMD effects of medroxyprogesterone acetate IM (Depo-Provera, DMPA) in adolescent females showed that its use was associated with a significant decline in BMD from baseline. In the small number of women who were followed-up, mean BMD recovered to around baseline values by 1-3 years after discontinuing treatment. In adolescents, Depo-Provera may be used, but only after other methods of contraception have been discussed with the patients and considered to be unsuitable or unacceptable.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years. In particular, in women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered prior to use of Depo-Provera.

Significant risk factors for osteoporosis include:
• Alcohol abuse and/or tobacco use
• Chronic use of drugs that can reduce bone mass, e.g. anticonvulsants or corticosteroids
• Low body mass index or eating disorder, e.g. anorexia nervosa or bulimia
• Previous low trauma fracture
• Family history of osteoporosis

A retrospective cohort study using data from the General Practice Research Database (GPRD) reported that women using MPA injections (DMPA), have a higher risk of fracture compared with contraceptive users with no recorded use of DMPA (incident rate ratio 1.41, 95% CI 1.35-1.47 for the
five year follow-up period); it is not known if this is due to DMPA, or to other related lifestyle factors which have a bearing on fracture rate. By contrast, in women using DMPA, the fracture risk before and after starting DMPA was not increased (relative risk 1.08, 95% CI 0.92-1.26). Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

- 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 amenorrhea.

- **Cancer Risks:** Long-term case-controlled surveillance of Depo-Provera users found no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer in the population of users. Breast cancer is rare among women under 40 years of age whether or not they use hormonal contraceptives. Results from some epidemiological studies suggest a small difference in risk of the disease in current and recent users compared with never-users. Any excess risk in current or recent DMPA users is small in relation to the overall risk of breast cancer, particularly in young women (see below), and is not apparent after 10 years since last use. Duration of use does not seem to be important. Possible number of additional cases of breast cancer diagnosed up to 10 years after stopping injectable progestogens*

<table>
<thead>
<tr>
<th>Age at last use of DMPA</th>
<th>No of cases per 10,000 women who are never-users</th>
<th>Possible additional cases per 10,000 DMPA users</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Less than 1</td>
<td>Much less than 1</td>
</tr>
<tr>
<td>30</td>
<td>44</td>
<td>2-3</td>
</tr>
<tr>
<td>40</td>
<td>160</td>
<td>10</td>
</tr>
</tbody>
</table>

*based on use for 5 years”

- DMPA IM injectable suspension has a prolonged contraceptive effect. The median time to contraception 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.

- **Anaphylaxis:** Reports of anaphylactic responses (anaphylactic reactions, anaphylactic shock, anaphylactoid reactions) have been received.

- **Thrombo-embolic Disorders:** Should the patient experience pulmonary embolism, cerebrovascular disease or retinal thrombosis while receiving Depo-Provera, the drug should not be re-administered
• **Hypertension and Lipid disorders**

Limited evidence suggests that there is a small increased risk of cardiovascular events among women with hypertension or with lipid disorders who used progestogen-only injectables. If hypertension occurs under depo-provera treatment and/or the increase in hypertension cannot adequately be controlled by antihypertensive medication, treatment with depo-provera should be stopped.

Additional risk factors for arterial thrombotic disorders include: Hypertension, smoking, age, lipid disorders, migraine, obesity, positive family history, cardiac valve disorders, atrial fibrillation.

depo-provera should be used cautiously in patients with one or more of these risk factors

• **Other conditions**

The following conditions have been reported both during pregnancy and during sex steroid use, but an association with the use of progestagens has not been established: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

• Patients should be counseled that DMPA injectable suspension does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

**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 should be alert to the earliest manifestations of thrombotic disorder (thrombophlebitis, cerebrovascular disorder, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

• The physician/laboratory should be informed that in addition to the endocrine biomarkers listed in Special Warnings and Special Precautions for Use (section 4.4), 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 amenorrhea and/or erratic menstrual patterns may follow the administration of either a single or multiple injectable dose of DMPA.

**Oral Formulations & 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 orally administered MPA or the 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).

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

Aminoglutethimide administered concurrently with Depo-Provera may significantly depress the bioavailability of Depo-Provera.

Interactions with other medicinal treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interaction should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of medroxyprogesterone acetate is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect the kinetics of medroxyprogesterone acetate. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

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.

3.6. 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. There is no definitive information for the other formulations of MPA, (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).

3.7. Effects on ability to drive and use machines

Depo-Provera may cause headaches and dizziness. Patients should be advised not to drive or operate machinery if affected.

3.8. Undesirable effects

CONTRACEPTION Intramuscular (IM) Formulation:

**Ear and Labyrinth Disorders**
- Uncommon: Vertigo

**Gastrointestinal Disorders**
- Very common: Abdominal pain or discomfort
- Common: Bloating, nausea
- Uncommon: Abdominal distension, gastrointestinal disturbances
- Rare: Rectal bleeding

**Infection & Infestations**
- Common: Vaginitis

**Metabolism & Nutrition Disorders**
- Common: Appetite decrease, appetite increase
- Uncommon: Weight increase, weight decrease, fluid retention

**Musculoskeletal, Connective Tissue & Bone Disorders**
- Common: Back pain
- Uncommon: Arthralgia, muscle cramps, pain in limbs
- Not known: Osteoporosis including osteoporotic fractures, loss of bone mineral density, axillary swelling

**Nervous System Disorders**
- Very common: Headaches
- Common: Dizziness
- Uncommon: Somnolence, migraine, convulsions
- Rare: Paralysis
- Not known: Syncope

**Reproductive System & Breast Disorders**
- Common: Amenorrhea, breast pain/tenderness, intermenstrual bleeding, menometrorrhagia, menorrhagia, pelvic pain, leucorrhoea
- Uncommon: Vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, premenstrual syndrome, genitourinary infection, uterine hyperplasia
- Rare: Breast lumps or nipple bleeding
- Not known: Abnormal uterine bleeding (irregular, increase, decrease), galactorrhea, vaginal cysts, prevention of lactation, sensation of pregnancy, lack of return to fertility

**Vascular Disorders**
- Common: Hot flushes
- Uncommon: Hypertension, varicose veins, thrombophlebitis, pulmonary embolism
- Not known: Thromboembolic disorders, deep vein thrombosis

**Cardiovascular Disorders**
- Rare: Tachycardia

**Immune System Disorders**
Uncommon: Hypersensitivity reactions (e.g. anaphylaxis & anaphylactoid reactions, angioedema)
Hepato-biliary disorders
Uncommon: Abnormal liver enzymes, jaundice
Not known: disturbed liver function
Skin & Subcutaneous Tissue Disorders
Common: Acne, alopecia, rash
Uncommon: Chloasma, dermatitis, ecchymosis, hirsutism, pruritus, melasma, urticaria, oedema
Not known: Skin striae, scleroderma
General Disorders and Administration Site Conditions
Common: Fatigue, injection site reactions (such as pain or abscess), asthenia, paraesthesia
Uncommon: Chest pain, pyrexia
Rare: Thirst, hoarseness, paralysis
Not known: Facial palsy
Investigations
Uncommon: Cervical smear abnormal
Rare: Decreased glucose tolerance
Psychiatric Disorders
Common: Anorgasmia, depression, nervousness, emotional disturbance, libido decreased, mood disorder, irritability, insomnia
Uncommon: Anxiety
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)
Rare: Breast cancer
Blood and lymphatic system disorders
Rare: Anaemia
Not known: Blood dyscrasia
Respiratory, thoracic, and mediastinal disorders
Uncommon: Dyspnoea

**ONCOLOGY**

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System disorders</td>
<td>Hypersensitivity reactions (e.g. anaphylaxis &amp; anaphylactoid reactions, angioedema)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation</td>
</tr>
<tr>
<td>Metabolism and nutritional disorders</td>
<td>Edema/fluid retention, weight change, exacerbation of diabetes mellitus</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Confusion, depression, euphoria, changes in libido, insomnia, nervousness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves in night)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision disorders, diabetic cataract, retinal thrombosis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Myocardial infarction, congestive heart failure, palpitations, tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thromboembolic disorders, thrombophlebitis</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal disorders</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation, diarrhea, dry mouth, nausea, vomiting</td>
</tr>
</tbody>
</table>
### 3.9. Overdose

Oral doses up to 3 g per day have been well tolerated. Overdose treatment is symptomatic and supportive.

### 4. PHARMACOLOGICAL PROPERTIES

#### 4.1. 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 results in endometrial thinning.

**Oncology**

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

**Clinical Studies**

**Bone Mineral Density Studies**

**BMD Changes in Adult Women**

In a controlled, clinical study adult women using DMPA injection (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller 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.

After stopping use of MPA injection (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery. (see Section 4.4 – Special warnings and precautions for use – Additional Warnings & Precautions for Specific Use or Formulation, Contraception/Endometriosis – Injectable Formulations, Loss of Bone Mineral Density).

**BMD Changes in Adolescent Females (12-18 years)**

An open-label non-randomized clinical study of DMPA injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1% after 240 weeks; mean decreases for the total hip and femoral neck were -6.4% and -5.4%, respectively. Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued and that hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4%, 1.7% and 1.9% for lumbar spine, total hip and femoral neck, respectively. (see Section 4.4 – Special warnings and precautions for use – Additional Warnings & Precautions for Specific Use or Formulation, Contraception/Endometriosis – Injectable Formulations, Loss of Bone Mineral Density).
Endometriosis Studies

The efficacy of DMPA-SC in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in two active comparator-controlled studies. Each study assessed reduction in endometriosis-associated pain over 6 months of treatment and recurrence of symptoms for 12-months post treatment. Subjects treated with DMPA-SC for 6 months received a 104 mg dose every 3 months (2 injections), while women treated with leuprolide microspheres for 6 months received a dose of 11.25 mg every 3 months (2 injections) or 3.75 mg every month (6 injections). Study 268 was conducted in the USA and Canada and enrolled 274 subjects (136 on DMPA-SC and 138 on leuprolide). Study 270 was conducted in South America, Europe and Asia, and enrolled 299 subjects (153 on DMPA-SC and 146 on leuprolide).

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhea, dyspareunia, and pelvic pain not related to menses) and two signs assessed during pelvic examination (pelvic tenderness and induration). For each category, a favorable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score (Figure 1).

![Figure 1. Percentages of Responders at End of Treatment (Month 6 or Last Assessment if Earlier) in Studies 268 & 270](image)

Favorable Response = reduction in severity of symptom or sign of $\geq$ 1 point on a scale of 0 to 3, as compared to baseline

Additionally, scores from each of the five categories were combined, with the total (composite score) considered a global measurement of overall disease improvement. For subjects with baseline scores for each of the 5 categories, a mean decrease of 4 points relative to baseline was considered a clinically meaningful improvement. Across both studies, for
both treatment groups, the mean changes in the composite score met the protocol-defined criterion for improvement.

In the clinical trials, treatment with DMPA-SC was limited to six months. Data on the persistence of benefit with longer treatment are not available.

Subjects recorded daily the occurrence and severity of hot flushes. Of the DMPA-SC users, 28.6% reported experiencing moderate or severe hot flushes at baseline, 36.2% at Month 3, and 26.7% at month 6. Of the leuprolide users, 32.8% reported experiencing moderate or severe hot flushes at baseline, 74.2% at Month 3, and 68.5% at Month 6.

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.)

4.2. Pharmacokinetic properties

Intramuscular formulations

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 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.

4.3. 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.
5. PHARMACEUTICAL PARTICULARS

5.1. List of excipients

**Depo Provera 150 mg/ml injection:** Water for Injection, Sodium Chloride, Macrogol 3000, Polysorbate 80, Methyl Paraben, Propyl Paraben, Sodium hydroxide, Hydrochloric acid.

**Depo Provera 500mg injection:** Water for Injection, Sodium Chloride, Macrogol 3350, Polysorbate 80, Methyl Paraben, Propyl Paraben, Sodium hydroxide, Hydrochloric acid.

5.2. Incompatibilities

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

5.3. Special precautions for storage

Store at room temperature, below 25°C.

5.4. Nature and contents of container

**Depo Provera 150 mg/ml:** 1 mL Injection as 150 mg/mL ready for use syringe

**Depo Provera 500:** 3.3 ml vial.

**Manufacturer:**

**Depo Provera 150 mg/ml, 500 injections:** Pfizer Manufacturing Belgium NV/SA

**License Holder:** Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Hertzliya Pituach, 46725