1. NAME OF THE MEDICINAL PRODUCT

DEPO-PROVERA™ Sterile aqueous suspension 50 mg/ml
DEPO-PROVERA™ Sterile aqueous suspension 150 mg/ml
DEPO-PROVERA™ Sterile aqueous suspension 500 mg
DEPO-PROVERA™ Sterile aqueous suspension 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-PROVERA™ Sterile aqueous suspension 50 mg/ml
Each ml contains:
Medroxyprogesterone acetate 50 mg - Polysorbate 80 - Methylparaben 1.30 mg -
Propylparaben 0.14 mg - Polyethylene glycol 3350 - Sodium chloride - Water for injection.

DEPO-PROVERA™ Sterile aqueous suspension 150 mg/ml
Each ml contains:
Medroxyprogesterone acetate 150 mg - Polysorbate 80 - Methylparaben 1.35 mg -
Propylparaben 0.15 mg - Polyethylene glycol 3350 - Sodium chloride - Water for injection.

DEPO-PROVERA™ Sterile aqueous suspension 500mg
Each ml contains:
Medroxyprogesterone acetate 500mg – 1000mg Polysorbate 80 - Methyl parahydroxybenz. -
Propyl parahydroxybenz. - Macrogol. 3350 - Natr. chlorid. - Aqua ad inieictabil.

DEPO-PROVERA™ Sterile aqueous suspension 1000mg
Each ml contains:
Medroxyprogesterone acetate 500mg – 1000mg Polysorbate 80 - Methyl parahydroxybenz. -
Propyl parahydroxybenz. - Macrogol. 3350 - Natr. chlorid. - Aqua ad inieictabil.

3. PHARMACEUTICAL FORM

FORMS
Sterile aqueous suspension.
WAYS OF ADMINISTRATION
Intramuscular administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEPO-PROVERA™ Sterile aqueous suspension is indicated:
1. For contraception (ovulation suppression).
2. In the treatment of endometriosis.
3. In the treatment of menopausal vasomotor symptoms.
4. As adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma.
5. In the treatment of hormonally-dependent, recurrent breast cancer in postmenopausal women.
Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use medroxyprogesterone acetate injection long-term (see section 4.4 Special warnings and special precautions for use), 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

CONTRACEPTION (ovulation suppression)
The recommended dose is 150 mg of DEPO-PROVERA™ Sterile aqueous suspension every three months administered by deep, intramuscular injection.
To increase assurance that the patient is not pregnant at the time of the first administration, it is recommended that this injection be given only during the first 5 days after the onset of a normal menstrual period; within 5 days postpartum if not breast-feeding; or, if breast-feeding, at 6 weeks postpartum.

ENDOMETRIOSIS
The recommended dose of DEPO-PROVERA™ Sterile aqueous suspension in this condition is 50 mg intramuscularly weekly or 100 mg every 2 weeks intramuscularly for at least 6 months. Patients should be warned that ovulation may be delayed after this treatment due to the prolonged activity of the medicine.

MENOPAUSAL VASOMOTOR SYMPTOMS
The recommended dose is 150 mg of DEPO-PROVERA™ sterile aqueous suspension administered intramuscularly every three months.

ENDOMETRIAL AND RENAL CARCINOMA
Doses of 400 mg to 1000 mg of DEPO-PROVERA™ Sterile aqueous suspension intramuscularly per week are 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
The recommended dosage schedule is DEPO-PROVERA Sterile aqueous suspension 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 is responding to treatment.

DIRECTIONS FOR USE
Vial
The vial should be vigorously shaken just before use to assure that the dose being administered represents a uniform suspension.
Syringe for single use
Shake thoroughly to obtain a uniform suspension.
1. Remove tip cap.
2. Fit the needle to the syringe.
3. In a sterile way position needle.
4. Remove needle shield. The syringe is now ready for use.

4.3 Contraindications
1. Known sensitivity to medroxyprogesterone acetate or any of the excipients.
2. Non-diagnosed vaginal bleeding
3. Non-diagnosed bleeding in the urinary tract
4. Non-diagnosed breast pathology or breast cancer
5. Pregnancy or suspected pregnancy
6. active thrombophlebitis or a history of thrombo-embolic disorders. The physician should look out for the first symptoms (thrombophlebitis, pulmonary embolism, cerebrovascular disorders and retinal thrombosis).
7. severe hepatic disease and hepatic function disorders

4.4 Special warnings and precautions for use

- Before using DEPO-PROVERA™ Sterile aqueous suspension, the status of the patient should be carefully evaluated. This evaluation should exclude the presence of genital or breast neoplasia before considering the use of DEPO-PROVERA™ Sterile aqueous suspension. This examination must be repeated each year. For those patients who will be receiving DEPO-PROVERA™ Sterile aqueous suspension for the treatment of endometrial, breast or renal cancer, the caution expressed by the preceding sentence does not apply. - Though DEPO-PROVERA™ Sterile aqueous suspension has not been causally associated with the induction of thromboembolic disorders, any patient who develops this kind of event while undergoing therapy with DEPO-PROVERA™. Sterile aqueous suspension should have her status and need for treatment carefully assessed before continuing therapy. - In the event of sudden onset of full or partial loss of vision, sudden proptosis, diplopia or migraine, patients must be re-evaluated before continuing treatment with DEPO-PROVERA™. DEPO-PROVERA™ must be discontinued if examination should reveal papilloedema or damage to the vessels of the retina.
- DEPO-PROVERA™ Sterile aqueous suspension, especially in the high doses used for cancer therapy, may cause weight gain and fluid retention. With this in mind, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by weight gain or fluid retention.
- The high doses of DEPO-PROVERA™ sterile aqueous suspension used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g. moon facies, fluid retention, glucose intolerance, and blood pressure elevation. - Though clinical inhibition of the adrenal cortical function has not been reported with the recommended contraceptive doses, corticosteroid-like effects have been noted with very high doses (500 mg per day or more). - Some patients receiving low dose DEPO-PROVERA™ Sterile aqueous suspension may exhibit a decreased glucose tolerance. The mechanism for this is not known. This fact should be borne in mind when treating all patients and especially known diabetics.
- Patients with a history of treatment for mental depression should be carefully monitored while receiving DEPO-PROVERA™ therapy. Some patients may complain of premenstrual like depression while on DEPO-PROVERA™ therapy; if a severe depression should develop again, the medication should be discontinued.
- Pathologists should be informed of the patients use of DEPO-PROVERA™ Sterile aqueous suspension if endometrial or endocervical tissue is submitted for examination.
- Aminoglutethimide administered concomitantly with DEPO-PROVERA™ Sterile aqueous suspension may significantly depress the bioavailability of DEPO-PROVERA™ Sterile aqueous suspension.
- Prolonged anovulation with amenorrhea and/or erratic menstrual patterns may follow the administration of either a single or multiple dose of DEPO-PROVERA™ Sterile aqueous suspension. After repeated injections, amenorrhoea and anovulation may last for up to 18 months and even longer in rare cases.
- In the event of non-diagnosed vaginal bleeding, adequate investigations are required. As is the case with all irregular bleeding, possible organic causes should be considered in the case of breakthrough bleeding.
- The physician/laboratory must be informed of the fact that the use of medroxyprogesterone acetate can lower the levels of the following endocrine biological markers:
  a. Plasma/urinary steroids (e.g. cortisol, oestrogen, pregnanediol, progesterone, testosterone)
  b. Plasma/urinary gonadotrophins (e.g. LH and FSH)
  c. Sex-hormone-binding globulin
- Anaphylactic and anaphylactoid reactions have been reported sporadically during treatment with DEPO-PROVERA™.
- Since progestogens may cause a certain amount of fluid retention, patients with conditions which might be influenced by this factor (e.g. epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.
- Administration of DEPO-PROVERA™ may mask the start of climacterium.
- Certain endocrine and possibly also liver function tests may be affected by the treatment with DEPO-PROVERA™.
- Treatment with DEPO-PROVERA™ may be associated with weight gain.

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

**Loss of Bone Mineral Density (BMD):** use of medroxyprogesterone acetate (MPA) injection reduces serum estrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of MPA injection by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after MPA injection is discontinued and production of estrogens of ovarian origin increases. A study to assess the reversibility of loss of BMD in adolescent females is ongoing.

MPA injection should only be used as a long-term (e.g., longer than 2 years) endometrial treatment if other endometrial treatments are inadequate. BMD should be evaluated when a female needs to continue to use MPA injection long term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.

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

**BMD Changes in Adult Women:**
In a controlled, clinical study adult women using MPA 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 partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery.
**BMD Changes in Adolescent Females (12-18 years):**
Preliminary results from an ongoing, open-label clinical study of MPA injectable (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that MPA IM use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

**Breast cancer:**
The use of combined oral oestrogens and progestogens by post-menopausal women has been reported to increase the risk of breast cancer. Results from a randomized placebo-controlled trial, the WHI (Women’s Health Initiative) trial, and epidemiological studies have indicated an increased risk of breast cancer in women taking oestrogens/progestogens combinations for hormone therapy for several years. In the WHI trial on the combined use of conjugated equine oestrogens (CEE) and medroxyprogesterone acetate and in the observation studies, the excess risk increased with duration of use (see section 4.2). The combined use of oestrogens and progestogens has also been reported to result in an increase in abnormal mammograms requiring further evaluation.

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

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

DEPO-PROVERA exerts a prolonged contraceptive effect. The mean time to conception for women who conceive is 10 months after the last injection, the range being from 4 to 31 months, and is not linked to the time during which the contraceptive has been used.
Patients should be informed that DEPO-PROVERA does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

If jaundice develops, interrupting the treatment must be considered.

4.5 Interaction with other medicinal products and other forms of interaction

The following laboratory test results may be affected by the use of DEPO-PROVERA™ Sterile aqueous suspension:

a. Gonadotropin levels.
b. Plasma progesterone levels.
c. Urinary pregnanediol levels.
d. Plasma testosterone levels (in the male).
e. Plasma estrogen levels (in the female).
f. Plasma cortisol levels.
g. Glucose tolerance test.
h. Metyrapone test.

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

Interactions with other medicines (including oral anticoagulants) have been reported in rare cases, but causality has not been established.

The clearance of medroxyprogesterone acetate is about equal to the hepatic blood flow. Consequently, medicines that induce hepatic enzymes are unlikely to influence the pharmacokinetics of medroxyprogesterone acetate. Therefore, no dose adjustment is recommended in patients treated with enzyme-inducing medicines.

A decrease in glucose tolerance has been observed in some patients treated with progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

4.6 Fertility, pregnancy and lactation

Medroxyprogesterone acetate is contra-indicated in pregnant women.

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

Unexpected pregnancies occurring one to two months following intramuscular administration of DEPO-PROVERA™ can result in low birth weight newborns, which is in turn associated with a higher risk of neonatal death. The attributable risk is low, as such pregnancies are uncommon.

If medroxyprogesterone acetate is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Progestational agents are also not recommended for use in lactating women before the 6th week postpartum.

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA™. In nursing mothers treated with DEPO-PROVERA™ contraceptive injection, milk composition, quality, and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioral effects through puberty. No adverse effects have been noted. See dosage and administration.
4.7 Effects on ability to drive and use machines

No data are available regarding the influence on ability to drive a vehicle and to use machinery. In view of the pharmacological profile of medroxyprogesterone acetate, no significant effect is to be expected.

4.8 Undesirable effects

The following adverse effects, listed according to the organ system they affect, have been sporadically, occasionally to rarely associated with the use of progestogens:

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urogenital system</td>
<td>Irregular menstruation (bleeding and amenorrhea or both), reduced libido or absence of orgasm, leucorrhoea, vaginitis, hot flushes, pelvic pain, abnormal uterine bleeding (irregular, increase, reduction) and prolonged anovulation, changes in cervical secretions, cervical erosions and extended anovulation.</td>
</tr>
<tr>
<td>Breasts</td>
<td>Breast tension, breast tenderness, mastodynia and galactorrhoea.</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Nervousness, insomnia, somnolence, fatigue, depression, dizziness and headaches, convulsions.</td>
</tr>
<tr>
<td>Gastrointestinal / Hepatobiliary</td>
<td>Cholestatic icterus/jaundice/hepatic function disorders, nausea, abdominal pain or discomfort, sensation of bloating.</td>
</tr>
<tr>
<td>Metabolism &amp; nutrition</td>
<td>Reduced glucose tolerance.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Thromboembolic disorders: thrombophlebitis and pulmonary embolism.</td>
</tr>
<tr>
<td>Skin and mucosa</td>
<td>Urticaria, pruritus, rash, acne, hirsutism and alopecia.</td>
</tr>
<tr>
<td>Allergies</td>
<td>Hypersensitivity reactions (e.g. anaphylaxis and anaphylactoid reactions, angioedema).</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>Reactions at the injection site: pain, residual lumps and change in skin color, asthenia, cramp in the legs, back pain, arthralgia, loss of bone mineral density.</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Hyperpyrexia, pyrexia, change in weight, weight gain, oedema/fluid retention, moon facies.</td>
</tr>
<tr>
<td>Urogenital system</td>
<td>Irregular menstruation (bleeding and amenorrhea or both), reduced libido or absence of orgasm, leucorrhoea, vaginitis, hot flushes, pelvic pain, abnormal uterine bleeding (irregular, increase, reduction) and prolonged anovulation, changes in cervical secretions, cervical erosions and extended anovulation.</td>
</tr>
</tbody>
</table>
In postmarketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients taking medroxyprogesterone acetate IM.

4.9 Overdose

Medroxyprogesterone acetate is very well tolerated. In the event of an overdose, this steroid may cause nausea and vomiting. Withdrawal bleeding may occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogen, ATC-code: G03DA02

Medroxyprogesterone acetate (17-alpha-hydroxy-6-alpha-methylprogesterone acetate) is a progestogen derived from progesterone.

After I.M. injection DEPO-PROVERA™ has a prolonged progestational action.

DEPO-PROVERA™ Sterile aqueous suspension is a progestational agent devoid of estrogenic activity. The androgenic activity on the other hand can be considered as minimal. DEPO-PROVERA™ Sterile aqueous suspension in appropriate doses suppresses the secretion of pituitary gonadotropsins which, in turn, prevents follicular maturation, producing anovulation in the reproductive-aged woman. It is probably due to this action that DEPO-PROVERA™ can alleviate vasomotor symptoms during the menopause.

DEPO-PROVERA™ Sterile aqueous suspension in appropriate doses suppresses the Leydig cell function in the male, i.e. suppresses endogenous testosterone production. A dose of either 5 or 10 mg of medroxyprogesterone acetate given daily for 10 days has the equivalent effect of 20 mg of parenteral progesterone given daily for 10 days in producing an optimal secretory change in an estrogen-primed endometrium. Oral medroxyprogesterone acetate also produces typical progestational changes in the cervical mucus (inhibits ferning), increases viscosity which impedes sperm penetration and increases the intermediate cell count in the maturation index of the vaginal epithelium.

The anti-cancer activity of DEPO-PROVERA™ Sterile aqueous suspension at pharmacologic doses in the case of specific forms of hormone-dependent cancers may be dependent upon its effect on the hypothalamic-pituitary-gonadal axis, estrogen receptors and the metabolism of steroids at the tissue level. Like progesterone, medroxyprogesterone acetate is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

5.2 Pharmacokinetic properties

Following intramuscular administration, medroxyprogesterone acetate (MPA) is slowly released, resulting in low, but persistent levels. Time to peak is approximately 4 to 20 days following an intramuscular dose. Circulating levels of MPA can be detected for as long as 7 to 9 months following an intramuscular injection. MPA is approximately 90 to 95% protein bound. Volume of distribution is reported as 20 ± 3 liters. MPA crosses the blood-brain-barrier and is secreted in breast milk. Numerous metabolites of MPA have been reported; however, these have not been well quantified. The elimination half-lives following intramuscular administration are 6 weeks. MPA is primarily excreted in the feces, via biliary secretion. Approximately 44% of unchanged drug is excreted in the urine.
5.3 Preclinical safety data
Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Not Applicable

6.2 Incompatibilities
DEPO PROVERA™ should not be mixed with any other agent.

6.3 Shelf life
Not Applicable

6.4 Special precautions for storage
Do not store above 25 °C.
The expiry date (month/year) is mentioned on the package after “EXP.:” (EXP. = expiry date).

6.5 Nature and contents of container
PACKAGES
DEPO-PROVERA™ Sterile aqueous suspension 50 mg/ml
1 ml, 3 ml and 5 ml vial.
DEPO-PROVERA™ Sterile aqueous suspension 150 mg/ml
1 ml and 10 ml vial; 1 ml disposable syringe.
DEPO-PROVERA™ Sterile aqueous suspension 500 mg
150 mg/ml in a 3.3 ml vial.
DEPO-PROVERA™ Sterile aqueous suspension 1000 mg
150 mg/ml in a 6.7 ml vial.

6.6 Special precautions for disposal <and other handling>
Not Applicable

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER
Pfizer SA., 17 Boulevard de la Plaine, 1050 Brussels, Belgium.

PACKED & RELEASED BY
Pfizer Manufacturing Belgium NV/SA - Puurs – Belgium

8. PRESCRIPTION STATUS
On medical prescription only.

9. DATE OF REVISION OF THE TEXT

April 2011