Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Depo-Provera 150 mg/ml Suspension for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 150mg of medroxyprogesterone acetate.
Excipients:
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Suspension for injection.

Product imported from Belgium:
White, sterile, aqueous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a progestogen, for parenteral administration:

Contraception
Depo-Provera is indicated for contraception.

Depo-Provera may also be used for short-term contraception in the following circumstances:
i. For partners of men undergoing vasectomy, for protection until the vasectomy becomes effective.
ii. In women who are being immunised against rubella, to prevent pregnancy during the period of activity of the virus.
iii. In women awaiting sterilisation.

Since loss of bone mineral density (BMD) may occur in females of all ages who use MPA 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.

It is of the greatest importance that adequate explanations of the long-term nature of the product, of its possible side effects and of the impossibility of immediately reversing the effects of each injection are given to potential users and that every effort is made to ensure that each patient receives such counselling as to enable her to fully understand these explanations. Patient information leaflets are supplied by the manufacturer. It is recommended that the doctor uses these leaflets to aid counselling of the patient.

Consistent with good clinical contraceptive practice a general medical as well as gynaecological examination should be undertaken before administration of Depo-Provera and at yearly intervals thereafter.

4.2 Posology and method of administration

The sterile aqueous suspension of Depo-Provera should be vigorously shaken just before use to ensure that the dose being given represents a uniform suspension of Depo-Provera.
Doses should be given by deep intramuscular injection into the gluteal muscle.

Contraception

All potential users of Depo-Provera should have a negative pregnancy test before first administration.
Because of the risk of heavy or prolonged bleeding in some women, the drug should be used with caution in the puerperium.

The recommended dose is 150 mg of MPA injectable suspension every 3 months administered by intramuscular injection in the gluteal muscle. The initial injection should be given during the first 5 days after the onset of a normal menstrual period; within 5 days postpartum if not breast-feeding; or, if exclusively breast-feeding, at or after 6 weeks postpartum.

As with other hormonal contraceptives, regular consideration should be given to whether the previous treatment has resulted in: first-time migraine or unusually severe headaches, visual disturbances, reappearance of depression, pathological changes in liver function tests.

Use in Children and Adolescents

MPA IM is not indicated before menarche.
Data regarding the effects of MPA on BMD in adolescent females (12-18 years) is available (see section 5.1 Pharmacodynamic Properties). Other than concerns about loss of BMD, the safety and effectiveness of MPA IM are expected to be the same for postmenarcheal adolescent and adult females

4.3 Contraindications

Depo-Provera is contraindicated in patients with a history of, or existent thrombo-embolic disorders; or at the above dosage with breast or genital cancer (known or suspected to be oestrogen dependent); and in patients with a known sensitivity to medroxyprogesterone acetate or any ingredient of the vehicle. Its use is contra-indicated in patients with impaired liver function or with active liver disease, and in patients with undiagnosed, vaginal bleeding.

Depo-Provera should not be used during known or suspected pregnancy, either for diagnosis or therapy

4.4 Special warnings and precautions for use

Warnings:
Loss of Bone Mineral Density

Use of 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 after discontinuation of MPA. It is unknown if use of MPA injection by adolescents and young adult 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 ovarian estrogen production increases.

MPA injection should only be used as a long-term (e.g., longer than 2 years) birth control method if other birth control methods are unsuitable. 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 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).
It is recommended that all patients have adequate calcium and Vitamin D intake.

For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to section 5.1 (Pharmacodynamic Properties)

Menstrual Irregularity
Prolonged anovulation with amenorrhoea and/or erratic menstrual patterns may follow the administration of either a single or multiple contraceptive doses of Depo-Provera. Unexpected vaginal bleeding during therapy with MPA should be investigated.

Return to fertility
Women should be counselled that there is a potential for delay in return to full fertility following use of Depo-Provera. The median time to conception for those who do conceive is 10 months following the last injection with a range of 4 to 31 months and is unrelated to the duration of use.

Cancer risks
Studies in animals have indicated that administration of very high doses of oestrogens and/or progestogens will induce neoplastic tumours in some animal species.

Studies in animals, in particular the dog, have demonstrated that the progestogens including progesterone will induce neoplastic mammary tumours. Recent investigations suggest that results of dosing studies with progestogen in the dog are irrelevant to the potential for such effects in human beings, because of differences in mammary receptor susceptibility and response.

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. A meta-analysis in 1996 from 54 epidemiological studies reported that there is a slight increased relative risk of having breast cancer diagnosed in women who are currently using hormonal contraceptives. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in hormonal contraceptive users, biological effects or a combination of both. The additional breast cancers diagnosed in current users of hormonal contraceptives or in women who have used them in the last ten years are more likely to be localised to the breast than those in women who never used hormonal contraceptives.

Breast cancer is rare among women under 40 years of age whether or not they use hormonal contraceptives. In the meta-analysis the results for injectable progestogens (1.5% of the data) and
progestogen only pills (0.8% of the data) did not reach significance although there was no evidence that they differed from other hormonal contraceptives. Whilst the background risk of breast cancer increases with age, the excess number of breast cancer diagnoses in current and recent injectable progestogen (IP) users is small in relation to the overall risk of breast cancer, possibly of similar magnitude to that associated with combined oral contraceptives. However, for IPs, the evidence is based on much smaller populations of users (less than 1.5% of the data) and is less conclusive than for combined oral contraceptives.

It is not possible to infer from these data whether it is due to an earlier diagnosis of breast cancer in ever-users, the biological effects of hormonal contraceptives, or a combination of reasons.

The most important risk factor for breast cancer in IP users is the age women discontinue the IP; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping IP use, such that by 10 years there appears to be no excess.

The evidence suggests that compared with never-users, among 10,000 women who use IPs for up to 5 years but stop by age 20, there would be much less than 1 extra case of breast cancer diagnosed up to 10 years afterwards. For those stopping by age 30 after 5 years use of the IP, there would be an estimated 2-3 extra cases (additional to the 44 cases of breast cancer per 10,000 women in this age group never exposed to oral contraceptives). For those stopping by age 40 after 5 years use, there would be an estimated 10 extra cases diagnosed up to 10 years afterwards (additional to the 160 cases of breast cancer per 10,000 never-exposed women in this age group).

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

Patients receiving treatment with progestogens should be kept under regular surveillance.

A very low incidence of anaphylactoid reactions has been reported.

Patients with a history of endogenous depression should be carefully monitored. Some patients may complain of premenstrual-type depression while on Depo-Provera therapy.

Precautions:

Medication should not be re administered pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine, jaundice or pathological changes in liver function tests. If examination reveals papilledema or retinal vascular lesions, medication should not be re administered.

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

Rare cases of thrombo-embolism have been reported with use of Depo-Provera. Should the patient experience pulmonary embolism, cerebrovascular disease or retinal thrombosis while receiving Depo-Provera, the drug should not be re administered.

Physicians should be aware that pathologists should be informed of the patient's use of Depo-Provera if endometrial or endocervical tissue is submitted for histologic examination. The results of certain laboratory tests may be affected by the use of Depo-Provera. These include plasma/urinary gonadotrophin levels (e.g. LH and FSH), plasma progesterone levels, urinary pregnanediol levels, plasma oestrogen levels (in the female), plasma cortisol levels, glucose tolerance test, metyrapone test, liver function tests, thyroid function tests and sex hormone binding globulin. Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX and X may increase.

The effects of medroxyprogesterone acetate on lipid metabolism have been studied with no clear impact demonstrated. Both increases and decreases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been observed in studies.

The drug should be used with caution in patients with cardiovascular or renal disease, asthma or epilepsy because of the potential problem of fluid retention in some patients.
There is a tendency for women to gain weight while on Depo-Provera therapy. Studies indicate that over the first 1-2 years of use, average weight gain was 5-8 lbs. Women completing 4-6 years of therapy gained an average of 14-16.5 lbs. There is evidence that weight is gained as a result of increased fat and is not secondary to an anabolic effect or fluid retention.
As with any intramuscular injection, especially if not administered correctly, there is a risk of abscess formation at the site of injection, which may require medical or surgical intervention.
Theoretical evidence suggests that use of progesterones should be interrupted for an interval to permit return to normal hypothalamo-pituitary-gonadal function. While it is not yet possible to state even a provisionally acceptable interval, any prescriber should bear this matter in mind when organising prolonged use of such agents.
As this product contains methylparahydroxybenzoate and propylparahydroxybenzoate, it may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglutethimide administered concurrently with Depo-Provera may significantly depress the bioavailability of Depo-Provera. Users of high-dose MPA should be warned of the possibility of decreased efficacy with the use of aminoglutethimide.

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

4.6 Pregnancy and lactation

Pregnancy
MPA is contraindicated in women who are pregnant.

Some reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses.

Infants from unintentional pregnancies that occur 1-2 months after injection of MPA injectable suspension may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. The attributable risk is low because pregnancies while on MPA are uncommon.

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

Children exposed to medroxyprogesterone acetate in utero and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development..

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. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects to puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Patients receiving Depo-Provera may be subject to the side-effects normally associated with the use of progestogens. In addition, it is likely that some or all of the following effects may occur.

Genitourinary
Delay in return to normal menstrual cycling and transient infertility lasting up to 18 months or occasionally longer may occur following continuous treatment with Depo-Provera.

i. Depo-Provera may be expected to cause disruption of the normal menstrual cycle. Irregular, prolonged, decreased or heavy vaginal bleeding or spotting may be experienced during the first two or three cycles of treatment. The frequency of occurrence of bleeding usually decreases with subsequent injections. After one year of treatment some women are amenorrhoeic.

BODY SYSTEM	EVENT
Genitourinary	Abnormal uterine bleeding (irregular, increase, decrease), amenorrhea, leukorrhea, pelvic pain, prolonged anovulation, vaginitis, decreased libido, anorgasmia.
Breast	Galactorrhea, mastodynia, tenderness
Central Nervous System	Convulsions, depression, dizziness, fatigue, headache, insomnia, nervousness, somnolence
Gastrointestinal/Hepatobiliary	Abdominal pain or discomfort, bloating, disturbed liver function, jaundice, nausea
Metabolic & Nutritional	Decreased glucose tolerance, weight change, fluid retention
Cardiovascular	Thromboembolic disorders
Skin & Mucous Membranes	Acne, hirsutism, pruritus, rash, urticaria, alopecia or no hair growth
Allergy	Hypersensitivity reactions (e.g. anaphylaxis and anaphylactoid reactions, angioedema)
Musculoskeletal	Arthralgia, asthenia, backache, injection-site reactions, leg cramps, loss of bone mineral density, osteoporosis*
Ocular	Sudden, partial or complete loss of vision, protopsis, diplopia, migraine, papilloedema or retinal vascular lesions.
Miscellaneous	Moon facies, hot flashes, pyrexia

*In postmarketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients taking MPA IM.

4.9 Overdose

No positive action is required other than cessation of therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Parenteral medroxyprogesterone acetate is a long acting progestational steroid. It exerts anti-oestrogenic, anti-androgenic and antigonadotrophic effects.

BMD Changes in Adult Women

In a controlled, clinical study adult women using MPA injection (150 mg IM) for up to 5 years 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) 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.

5.2 Pharmacokinetic properties

The drug is absorbed readily, metabolised in the liver initially to progesterone which is rapidly distributed to binding sites, and to pregnanediol and excreted thereafter in urine.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients present in the product imported from Belgium
Polysorbate 80
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Macrogol 3350
Sodium chloride
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.

6.5 Nature and contents of container

1 ml pre-filled disposable syringe consisting of a Type I (Ph. Eur.) glass barrel with a butyl rubber stopper and tip cap containing 1 ml of suspension.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Do not mix with other agents. For single use only. Discard any unused contents.

7 Parallel Product Authorisation Holder

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 Parallel Product Authorisation Number

PPA 0465/175/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 07 April 2006

10 DATE OF REVISION OF THE TEXT

October 2008