SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Depo-Provera 150 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of suspension contains 150 mg medroxyprogesterone acetate

Excipients with known effect:
Methyl parahydroxybenzoate (E218) – 1.35 mg
Propyl parahydroxybenzoate (E216) – 0.15 mg
Polysorbate 80 – 2.4 mg per mL

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sterile suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Progestogen: for contraception.

Depo-Provera is indicated for long-term female contraception. Each injection prevents ovulation and provides contraception for at least 12 weeks (+/- 5 days). However, it should be taken into consideration that the return to fertility (ovulation) may be delayed for up to one year (see section 4.4).

Depo-Provera is suitable for use in women who have been appropriately counselled concerning the likelihood of menstrual disturbance and the potential for a delay in return to full fertility.

Depo-Provera may also be used for short-term contraception in the following circumstances:

1) For partners of men undergoing vasectomy, for protection until the vasectomy becomes effective.
2) In women who are being immunised against rubella, to prevent pregnancy during the period of activity of the virus.
3) In women awaiting sterilisation.

Since loss of bone mineral density (BMD) may occur in females of all ages who use Depo-Provera injection long-term (see section 4.4), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during

pregnancy and/or lactation, should be considered before giving the injection of Depo-Provera.

Paediatric population (12-18 years)

In adolescents, Depo-Provera may be used, but **only** after other methods of contraception have been discussed with the patient and considered unsuitable or unacceptable.
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 before giving the injection of Depo-Provera.

4.2 Posology and method of administration

Posology

Adults:

First injection: To provide contraceptive cover in the first cycle of use, an injection of 150 mg i.m. should be given during the first five days of a normal menstrual cycle. If the injection is carried out according to these instructions, no additional contraceptive cover is required.

Post Partum: To increase assurance that the patient is not pregnant at the time of first administration, this injection should be given within 5 days post partum if not breast-feeding.

There is evidence that women prescribed Depo-Provera in the immediate puerperium can experience prolonged and heavy bleeding. Because of this, the drug should be used with caution in the puerperium. Women who are considering use of the product immediately following delivery or termination should be advised that the risk of heavy or prolonged bleeding may be increased. Doctors are reminded that in the non breast-feeding, post partum patient, ovulation may occur as early as week 4.

If the puerperal woman will be breast-feeding, the initial injection should be given no sooner than six weeks post partum, when the infant's enzyme system is more fully developed. Further injections should be given at 12 week intervals.

Further doses: 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 five 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 fourteen days after this subsequent injection.

Elderly: Not appropriate.

Paediatric population:
Depo-Provera is not indicated before menarche (see section 4.1 Therapeutic Indications).

Data in adolescent females (12-18 years) is available for IM administration of medroxyprogesterone acetate (MPA) (see Section 4.4 Special Warnings and Precautions for Use and section 5.1 Pharmacodynamic properties). Other than concerns about loss of BMD, the safety and effectiveness of Depo-Provera is expected to be the same for adolescents after menarche and adult females.

Switching from other Methods of Contraception

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

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).

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.

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. Care should be taken to ensure that the depot injection is given into the muscle tissue, preferably the gluteus maximus, but other muscle tissue such as the deltoid may be used.

The site of injection should be cleansed using standard methods prior to administration of the injection.

4.3 Contraindications

Hypersensitivity to medroxyprogesterone acetate or to any of excipients listed in section 6.1.

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

Depo-Provera is contraindicated as a contraceptive at the above dosage in known or suspected hormone-dependent malignancy of breast or genital organs.

Depo-Provera is contraindicated in patients with the presence or history of severe hepatic disease whose liver function tests have not returned to normal.

Whether administered alone or in combination with oestrogen, Depo-Provera should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital tract malignancy eliminated.

Depo-Provera is contraindicated in patients with meningioma or history of meningioma.

4.4 Special warnings and precautions for use

Assessment of women prior to starting hormonal contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

Loss of Bone Mineral Density:
Use of depot medroxyprogesterone acetate intramuscular (DMPA-IM) 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 DMPA-IM 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 DMPA-IM by younger women will reduce peak bone mass and increase the risk for fracture in later life i.e. after menopause.

A study to assess the BMD effects of DMPA-IM (Depo-Provera) in adolescent females showed that its use was associated with a statistically significant decline in BMD from baseline. After discontinuing DMPA-IM in adolescents, return of mean BMD to baseline values 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). However in some participants, BMD did not fully return to baseline during follow-up and the long-term outcome is not known in this group. 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.

A large observational study of predominantly adult female contraceptive users showed that use of DMPA-IM did not increase risk for bone fractures. Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life (see section 5.1 – Relationship of fracture incidence to use of DMPA-IM by women of reproductive age).

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

For further information on BMD changes in both adult and adolescent females, refer to section 5.1.

Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Menstrual Irregularity: The administration of Depo-Provera usually causes disruption of the normal menstrual cycle. Bleeding patterns include amenorrhoea (present in up to 30% of women during the first 3 months and increasing to 55% by month 12 and 68% by month 24); irregular bleeding and spotting; prolonged (>10 days) episodes of bleeding (up to 33% of women in the first 3 months of use decreasing to 12% by month 12). Rarely, heavy prolonged bleeding may occur. Evidence suggests that prolonged or heavy bleeding requiring treatment may occur in 0.5-4 occasions per 100 women years of use. If abnormal bleeding persists or is severe, appropriate investigation should take place to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary. Excessive or prolonged bleeding can be controlled by the co-administration of oestrogen. This may be delivered either in the form of a low dose (30 micrograms oestrogen) combined oral contraceptive pill or in the form of oestrogen replacement therapy such as conjugated equine oestrogen (0.625-1.25 mg daily). Oestrogen therapy may need to be repeated for 1-2 cycles. Long-term co-administration of oestrogen is not recommended.

Return to Fertility: There is no evidence that Depo-Provera causes permanent infertility. Pregnancies have occurred as early as 14 weeks after a preceding injection, however, in clinical trials, the mean time to return of ovulation was 5.3 months following the preceding injection. Women should be counselled that there is a potential for delay in return to full fertility following use of the method, regardless of the duration of use, however, 83% of women may be expected to conceive within 12 months of the first "missed" injection (i.e. 15 months after the last injection administered). The median time to conception was 10 months (range 4-31) after the last injection.

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*

Age at last use of DMPA	No of cases per 10,000 women who are never-users	Possible additional cases per 10,000 DMPA users
20	Less than 1	Much less than 1
30	44	2-3
40	160	10

*based on use for 5 years"

Meningioma: Cases of meningioma (single and multiple) have been reported in patients treated with
medroxyprogesterone acetate for a prolonged time (several years). If a patient is diagnosed with meningioma, medroxyprogesterone acetate must be stopped, as a precautionary measure.
In some cases, shrinkage of meningioma was observed after treatment discontinuation of depot medroxyprogesterone acetate.

Weight Gain: 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.

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.

Psychiatric Disorders: Patients with a history of endogenous depression should be carefully monitored. Some patients may complain of premenstrual-type depression while on Depo-Provera therapy.
Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use
(see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and
suicide. Women should be advised to contact their physician in case of mood changes and depressive
symptoms, including shortly after initiating the treatment.

Abscess formation: 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 and/or surgical intervention.

Precautions:
History or emergence of the following conditions require careful consideration and appropriate investigation: migraine or unusually severe headaches, acute visual disturbances of any kind, pathological changes in liver function and hormone levels. Patients with thromboembolic or coronary vascular disease should be carefully evaluated before using Depo-Provera.

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 monitored while receiving progestogen therapy.

Rare cases of thrombo-embolism have been reported with use of Depo-Provera, but causality has not been established.

The effects of medroxyprogesterone acetate on lipid metabolism have been studied with no clear impact demonstrated. Both increases and decreases in total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol have been observed in studies.
The use of Depo-Provera appears to be associated with a 15-20% reduction in serum high density lipoprotein (HDL) cholesterol levels which may protect women from cardiovascular disease. The clinical consequences of this observation are unknown. The potential for an increased risk of coronary disease should be considered prior to use.

Doctors should carefully consider the use of Depo-Provera in patients with recent trophoblastic disease before levels of human chorionic gonadotrophin have returned to normal.

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 examination.

The results of certain laboratory tests may be affected by the use of Depo-Provera. These include gonadotrophin levels (decreased), plasma progesterone levels (decreased), urinary pregnanediol levels (decreased), plasma oestrogen levels (decreased), plasma cortisol levels (decreased), glucose tolerance test, metyrapone test, liver function tests (may increase), thyroid function tests (protein bound iodine levels may increase and T3 uptake levels may decrease). Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX and X may increase.

Women should be counselled that Depo-Provera does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS). Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

The benefits of contraceptive options and their risks must be evaluated individually for each woman.If any of the conditions/risk factors mentioned is present, the benefits of Depo-Provera use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether Depo-Provera use should be discontinued.

<u>Excipient information:</u>
As this product contains methylparahydroxybenzoate and propylparahydroxybenzoate, it may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

Depo-provera contains less than 1 mmol sodium (23 mg) per pre-filled syringe or vial, that is to say essentially ‘sodium-free’.

Depo-Provera contains polysorbate 80 (see section 2). Polysorbate 80 may cause

hypersensitivity reactions.

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.

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.

4.6 Fertility, pregnancy and lactation

Fertility
MPA at oral doses may inhibit ovulation.

Women may experience a delay in return to fertility (conception) following discontinuation of Provera.

Pregnancy
Provera 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 foetuses.
If Provera 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 foetus.

Infants from unintentional pregnancies that occur 1 to 2 months after injection of medroxyprogesterone acetate 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 medroxyprogesterone acetate are uncommon.

Breast-feeding
Medroxyprogesterone acetate and its metabolites are secreted in breast milk.
In nursing mothers treated with medroxyprogesterone acetate injection 150 mg IM every 3 months, milk composition, quality, and amount are not adversely affected
Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.
However, due to limitations of the data regarding the effects of MPA in breastfed infants less than six weeks old, Provera should be given no sooner than six weeks post-partum when the infant's enzyme system is more developed.

4.7 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.

4.8 Undesirable effects

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%).

The following lists of adverse reactions are listed within the organ system classes, under headings of frequency (number of patients expected to experience the reaction), using the following categories:
Very common (≥1/10)
Common (≥1/100 to <1/10);
Uncommon (≥1/1000 to <1/100);
Rare (≥1/10,000 to <1/1000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data)

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 the available data)**
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)				Breast cancer	Meningioma
Blood and lymphatic system disorders				Anaemia, Blood disorder	
Immune system disorders			Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction, Angioedema	
Metabolism & Nutrition Disorder			Increased appetite, decreased appetite		
Psychiatric disorders	Nervousness	Depression, Libido decreased	Insomnia	Anorgasmia, Emotional disturbance, Effective disorder, Irritability, Anxiety	

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 the available data)
Nervous system disorders	Headache	Dizziness	Seizure, Somnolence, Paraesthesia	Migraine, Paralysis, Syncope	
Ear and Labyrinth Disorder				Vertigo	
Cardiac disorder				Tachycardia	
Vascular disorders			Hot flush	Embolism and thrombosis, Deep vein thrombosis, Thrombophlebitis, Hypertension, Varicose veins	
Respiratory, thoracic, and mediastinal disorders			Dyspnoea	Pulmonary embolism	
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort	Nausea, Abdominal distension		Rectal haemorrhage, Gastrointestinal disorder	
Hepatobiliary disorders			Hepatic function abnormal	Jaundice, Hepatic enzyme abnormal	
Skin and subcutaneous tissue disorders		Alopecia, Acne, Rash	Hirsutism, Urticaria, Pruritus, Chloasma	Lipodystrophy acquired*, Dermatitis, Ecchymosis, Scleroderma, Skin striae	
Musculoskeletal and connective tissue disorders		Back pain, Pain in extremity		Arthralgia, Muscle spasms, Osteoporosis, Osteoporotic fractures	

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 the available data)
Reproductive system and breast disorders		Vaginal discharge, Breast tenderness, Dysmenorrhea, Genitourinary tract infection	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting, Galactorrhoea Pelvic pain, Dyspareunia, Suppressed lactation	Vaginitis, Amenorrhoea, Breast pain, Metrorrhagia, Menometrorrhagia, Menorrhagia, Vulvovaginal dryness, Breast atropy, Ovarian cyst, Premenstrual syndrome, Endometrial hyperplasia, Breast mass, Nipple exudate bloody, Vaginal cyst, Breast enlargement, Lack of return to fertility, Sensation of pregnancy	
General disorders and administration site conditions		Odema/Fluid retention, Asthenia	Chest pain	Pyrexia, Fatigue, Injection site reaction*, Injection site persistent atrophy/indentation/dimpling*, Injection site nodule/lump*, Injection site pain/tenderness * Thirst, Dysphonia, VIIth nerve paralysis, Axillary swelling	

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 the available data)
Investigation	Weight increased, Weight decreased			Bone density decreased, Glucose tolerance decreased, Cervical smear abnormal	

*ADR identified post-marketing

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No positive action is required other than cessation of therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens, ATC code: G03AC06

Medroxyprogesterone acetate exerts anti-oestrogenic, anti-androgenic and antigonadotrophic effects.

Mechanism of action
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.

BMD Changes in Adult Women

A study comparing changes in BMD in women using DMPA SC with women using DMPA-IM showed similar BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the DMPA-SC group are listed in Table 1.

Table 1. Mean Percent Change (with 95% Confidence Intervals) from Baseline in BMD in Adult Women Using DMPA-SC by Skeletal Site

Time on Treatment	Lumbar Spine		Total Hip		Femoral Neck	
	N	Mean % Change (95% CI)	N	Mean % Change (95% CI)	N	Mean % Change (95% CI)
1 year	166	-2.7 (-3.1 to -2.3)	166	-1.7 (-2.1 to -1.3)	166	-1.9 (-2.5 to -1.4)
2 year	106	- 4.1 (-4.6 to -3.5)	106	-3.5 (-4.2 to -2.7)	106	-3.5 (-4.3 to -2.6)

CI = Confidence Interval

In another controlled, clinical study adult women using DMPA-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 –2.9%, -4.1%, -4.9%, -4.9% and –5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 2 below for further details.

After stopping use of DMPA-IM, BMD increased towards baseline values during the post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery.

In the same clinical study, a limited number of women who had used DMPA-IM for 5 years were followed-up for 2 years after stopping DMPA-IM use. BMD increased towards baseline values during the 2-year post-therapy period. Two years after stopping DMPA injections, mean BMD had increased at all 3 skeletal sites but deficits remained (see Table 2 below).

Table 2. Mean Percent Change (with 95% Confidence Intervals) from Baseline in BMD in Adults by Skeletal Site and Cohort after 5 Years of Therapy with DMPA-IM and after 2 Years Post-Therapy or 7 Years of Observation (Control)

Time in Study	Spine		Total Hip		Femoral Neck	
	DMPA	Control	DMPA	Control	DMPA	Control
5 years* n Mean (SD) 95% CI	33 -5.4% (3.57) -6.65; -4.11	105 0.4% (3.27) -0.20; 1.06	21 -5.2% (3.60) -6.80; -3.52	65 0.2% (3.18) -0.60; 0.98	34 -6.1% (4.68) -7.75; -4.49	106 -0.3% (5.22) -1.27; 0.73
7 years** n Mean (SD) 95% CI	12 -3.1% (3.15) -5.13; -1.13	60 0.5% (3.65) -0.39; 1.49	7 -1.3% (4.95) -5.92; 3.23	39 0.9% (3.81) -0.29; 2.17	13 -5.4% (2.73) -7.03; -3.73	63 -0.0% (5.88) -1.51; 1.45

*The treatment group consisted of women who received DMPA-IM for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received DMPA-IM for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.
SD = Standard Deviation
CI = Confidence Interval

BMD Changes in Adolescent Females (12-18 years)
Results from an open-label, non-randomised, clinical study of DMPA-IM (150 mg IM every 12 weeks for up to 240 weeks (4.6 years), followed by post–treatment measurements) in adolescent females (12-18 years) also showed that medroxyprogesterone acetate IM use was associated with 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 (4.6 years); mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. Please refer to table 3. In contrast, a non-comparable cohort of unmatched, untreated subjects, with different baseline bone parameters from the DMPA users, showed mean BMD increases at 240 weeks of 6.4%, 1.7% and 1.9% for lumbar spine, total hip and femoral neck, respectively.

Table 3. Mean Percent Change (with 95% Confidence Intervals) from Baseline in BMD in Adolescents Receiving ≥4 Injections per 60-week Period, by Skeletal Site

Duration of Treatment	**DMPA-IM**	
	N	**Mean % Change [95 % CI]**
Total Hip BMD		
Week 60 (1.2 years)	113	-2.7 [-3.27; -2.12]
Week 120 (2.3 years)	73	-5.4 [-6.16; -4.64]
Week 180 (3.5 years)	45	-6.4 [-7.38; -5.37]
Week 240 (4.6 years)	28	-6.4 [-8.56; -4.24]
Femoral Neck BMD		
Week 60	113	-2.9 [-3.72; -2.15]
Week 120	73	-5.3 [-6.23; -4.37]
Week 180	45	-6.0 [-7.31; -4.59]
Week 240	28	-5.4 [-7.81; -3.00]
Lumbar Spine BMD		
Week 60	114	-2.5 [-2.95; -1.98]
Week 120	73	-2.7 [-3.57; -1.91]
Week 180	44	-2.7 [-3.99; -1.35]
Week 240	27	-2.1 [-4.16; -0.07]

CI = Confidence Interval

Post-treatment follow-up of adolescent participants from the same study, who received at least 1 DMPA injection and provided at least 1 follow-up BMD measurement after stopping DMPA-IM use is shown in Table 4. The median number of injections received in this cohort during the treatment phase was 9. At the time of the final DMPA injection, BMD % changes from baseline in this cohort were -2.7%, -4.1% and -3.9% at the spine, total hip and femoral neck, respectively. Over time, these mean BMD deficits recovered to baseline after DMPA-IM was discontinued. Recovery to baseline required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck. However, it is important to note that a large number of subjects discontinued from the study, therefore these results are based on a small number of subjects and some subjects still had deficit in total hip BMD after

240 weeks. Longer duration of treatment and smoking were associated with slower recovery. Please refer to Table 4 below.

Table 4. Mean Percentage Changes (with 95% Confidence Intervals) from Baseline in BMD in Adolescents after Discontinuation of DMPA

Week after DMPA discontinuation	N	Median Number of injections	Mean % change (SE) from baseline to end of treatment	95% CI	Mean % change (SE) from baseline to post-DMPA visit	95% CI
Total Hip BMD						
0	98	9	-4.1 (0.43)	[-4.95; -3.25]	N/A	
24	74	9	-4.1 (0.53)	[-5.15; -3.04]	-4.0 (0.61)	[-5.25; -2.80]
60	71	8	-3.6 (0.46)	[-4.48; -2.66]	-2.8 (0.56)	[-3.97; -1.72]
120	52	10	-4.3 (0.64)	[-5.56; -2.98]	-1.7 (0.72)	[-3.14; -0.26]
180	39	7	-4.1 (0.72)	[-5.55; -2.63]	-1.2 (0.85)	[-2.96; 0.46]
240	25	9	-3.4 (0.67)	[-4.73; -1.98]	0.1 (0.98)	[-1.95; 2.11]
Femoral Neck BMD						
0	98	9	-3.9 (0.50)	[-4.92; -2.92]	N/A	
24	74	9	-3.8 (0.60)	[-5.01; -2.62]	-4.0 (0.71)	[-5.40; -2.55]
60	71	8	-3.3 (0.56)	[-4.41; -2.18]	-3.6 (0.70)	[-4.99; -2.18]
120	52	10	-3.8 (0.74)	[-5.25; -2.28]	-1.8 (0.82)	[-3.43; -0.13]
180	39	7	-3.9 (0.85)	[-5.62; -2.17]	-1.0 (0.98)	[-3.00; 0.97]
240	25	9	-3.4 (0.80)	[-5.07; -1.78]	-0.7 (1.19)	[-3.20; 1.72]
Lumbar Spine BMD						
0	98	9	-2.7 (0.39)	[-3.45; -1.91]	N/A	
24	74	9	-2.6 (0.43)	[-3.42; -1.69]	-2.5 (0.51)	[-3.52; -1.48]
60	70	8	-2.8 (0.43)	[-3.66; -1.96]	-0.2 (0.60)	[-1.41; 1.01]
120	52	10	-2.7 (0.61)	[-3.96; -1.50]	2.2 (0.73)	[0.74; 3.67]
180	39	7	-3.0 (0.67)	[-4.35; -1.66]	2.8 (0.79)	[1.16; 4.35]
240	25	9	-2.6 (0.80)	[-4.28; -0.99]	4.5 (1.03)	[2.35; 6.61]

SE = Standard Error
CI = Confidence Interval

<u>Relationship of Fracture Incidence to Use of DMPA-IM (150 mg) by Women of Reproductive Age</u>

A large retrospective cohort study using data from the General Practice Research Database (GPRD) included N=41,876 women who used DMPA for contraception and had data available for 6-24 months before their first use of DMPA and for mean 5.5 years after their first DMPA injection. Fracture risk was observed to be higher overall in the DMPA cohort when compared to non users both 'before' and 'after' DMPA use. Fracture risk was compared between the period 'after' first DMPA injection vs. the period 'before' first injection: Incident Risk Ratio=1.01 (95% CI: 0.92, 1.11), suggesting that DMPA did not increase risk for bone fracture.

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. Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life i.e. following the menopause.

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 - Systeme National des Donnees de Sante) 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/3ml 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 to 13.56)). This excess risk seems to be driven primarily by prolonged use (≥3 years) of medroxyprogesterone acetate.

5.2 Pharmacokinetic properties

Parenteral medroxyprogesterone acetate (MPA) is a long acting progestational steroid. The long duration of action results from its slow absorption from the injection site. Immediately after 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. Concentrations fell to the initial levels by the end of 12 weeks. At lower doses, plasma levels of MPA appear directly related to the dose administered. Serum accumulation over time was not demonstrated. MPA is eliminated via faecal and urinary excretion. Plasma half-life is about six weeks after a single intramuscular injection. At least 11 metabolites have been reported. All are excreted in the urine, some, but not all, conjugated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Medroxyprogesterone acetate has been shown to have adverse effects on reproduction in animals and is contraindicated for use during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Macrogol 3350
Polysorbate 80
Propyl parahydroxybenzoate (E216)
Sodium chloride
Hydrochloric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Syringe: 3 years.
Vial: 5 years.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.
Vial: store upright.

6.5 Nature and contents of container

1 ml suspension for injection in a pre-filled glass syringe with halobutyl rubber plunger stopper and halobutyl rubber tip cap, packed singly.

1 ml suspension for injection in glass vials with halobutyl rubber stopper and aluminum cap with a plastic flip off in pack sizes of 1 or 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/0965

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 27 August 1991
Date of latest renewal: 08 January 2009

10 DATE OF REVISION OF THE TEXT

19/09/2025