Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Depo-Provera 150 mg/ml Suspension for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 1 ml of suspension containing 150 mg medroxyprogesterone acetate.

Excipients with known effect:
Methyl parahydroxybenzoate (E218) – 1.35 mg,
Propyl parahydroxybenzoate (E216) – 0.15 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.
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:

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 depot-medroxyprogesterone acetate (DMPA) 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.

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.

It should be taken into consideration that the return to fertility (ovulation) may be delayed for up to one year (see section 4.4).

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

Posology

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 DMPA injectable suspension every 3 months (12-13 weeks) administered by intramuscular injection in the gluteal or deltoid muscle. The gluteal muscle is the optimal site, however the deltoid muscle may be used if sufficiently well developed. 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.

For 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.

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.

Paediatric population

DMPA IM is not indicated before menarche.

Data in adolescent females (12-18 years) is available for IM administration of MPA (see section 4.4 and section 5.1). Other than concerns about loss of BMD, the safety and effectiveness of DMPA-IM are expected to be the same for adolescents after menarche and adult females.

Switching from other Methods of Contraception

When switching from other contraceptive methods, (DMPA IM or SC) 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).

Hepatic Insufficiency

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of DMPA. 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).

Renal Insufficiency

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of DMPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment should be necessary in women with renal insufficiency.

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 or deltoid muscle. The gluteal muscle is the optimal site if sufficiently well developed.

4.3 Contraindications

Depo-Provera is contraindicated in patients

- with a history of, or existent thrombo-embolic disorders

- with breast or genital cancer (known or suspected to be oestrogen dependent) at the above dosage
- Hypersensitive to medroxyprogesterone acetate or to any of the excipients listed in section 6.1
- with impaired liver function or with active liver disease
- with undiagnosed, vaginal bleeding.
- with severe liver dysfunction
- known or suspected to be pregnant, either for diagnosis or therapy.

4.4 Special warnings and precautions for use

Warnings:
Loss of Bone Mineral Density (BMD)
Use of depot medroxyprogesterone acetate IM (DMPA-IM) injection reduces serum oestrogen levels and is associated with significant loss of BMD due to 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

Bone Fracture
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 adultfemale 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, as reported in recent clinical studies, 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
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 DMPA 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.

Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, when used as directed, will not expose them to STIs. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

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.
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.

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.

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.
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.

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

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

Medroxyprogesterone acetate (DMPA) 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

Pregnancy
DMPA 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.

Infants from unintentional pregnancies that occur 1-2 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.

If DMPA 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 foetus.

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
DMPA 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 acetate 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 relevant.

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.

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.

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
Immune system disorders			Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Endocrine disorders				Prolonged anovulation, Moon Face
Psychiatric disorders	Nervousness	Depression, Libido decreased	Insomnia	Anorgasmia
Nervous system disorders	Headache	Dizziness	Seizure, Somnolence	Migraine
Eye Disorder				Loss of vision (sudden, partial or complete), Exophthalmos, Diplopia, Papilloedema, Retinal embolism and thrombosis
Vascular disorders			Hot flush	Embolism and thrombosis
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort	Nausea, Abdominal distension		
Hepatobiliary disorders			Liver disorder	Jaundice
Skin and subcutaneous tissue disorders		Alopecia, Acne, Rash	Hirsutism, Urticaria, Pruritus	Lipodystrophy acquired*
Musculoskeletal and connective tissue disorders		Back pain		Arthralgia, Muscle spasms, Osteoporosis**
Reproductive system and breast disorders		Vaginal discharge, Breast tenderness	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting, Galactorrhoea Pelvic pain	Vaginitis, Amenorrhoea, Breast pain
General disorders and administration site conditions		Fluid retention, Asthenia		Pyrexia, Fatigue, Injection site reaction*, Injection site persistent atrophy/indentation/dimpling*, Injection site nodule/lump*, Injection site pain/tenderness*
Investigation	Weight increased, Weight decreased			Bone density decreased, Glucose tolerance decreased

*ADR identified post-marketing

**In post-marketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients taking DMPA IM.

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 HPRA Pharmacovigilance; Website: www.hpra.ie.

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,

Parenteral medroxyprogesterone acetate is a long acting progestational steroid. It 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 toward 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).

Table2. 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 DPMA-IM for 5 years and the control group consisted of women who did not use a 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 a 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-randomized 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 DMPA-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

Relationship of Fracture Incidence to Use of DMPA-IM (150 mg) by Women of Reproductive Age
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.

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.

Absorption: Following intramuscular administration, DMPA 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: DMPA 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)Low levels of medroxyprogesterone acetate have been detected in breast milk of lactating women (see section 4.6)administered 150 mg of medroxyprogesterone acetate by the IM route.

Metabolism: DMPA 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 faeces, via biliary secretion. Approximately 30 % of an intramuscular dose is secreted in the urine after 4 days.

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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 and other handling

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland

9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
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8 MARKETING AUTHORISATION NUMBER

PA0822/124/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th January 1996
Date of last renewal: 19th January 2006

10 DATE OF REVISION OF THE TEXT

June 2021