1.3.1 Summary of product characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Medogen 150 mg/ml Suspension for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of suspension contains 150 mg medroxyprogesterone acetate
Each mL contains

- Methyl paraben 1.37 mg
- Propyl paraben 0.15 mg
- Sodium chloride (8.68 mg) equivalent to 3.41 mg (0.15 mmol) sodium

This medicine contains less than 1 mmol sodium, that is to say, is essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile suspension for injection.
White to off-white, sterile suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Medogen 150 mg/ml Suspension for Injection (DMPA) is used for long-term contraception in women aged over 18 years.

It can also be used for short-term contraception to cover specific periods when:

- the woman's male partner is awaiting vasectomy to become effective;
- the woman is awaiting sterilization;
- the woman at risk of rubella is awaiting immunization against rubella.

Medogen 150 mg/ml Suspension for Injection may be used in adolescents aged over 12 years if there is compelling reason for contraception and other methods are unsuitable or unacceptable.

Since loss of bone mineral density (BMD) may occur in females of all ages who use Medogen 150 mg/ml Suspension for Injection long-term (see section 4.4), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy or lactation, should be considered before giving Medogen 150 mg/ml Suspension for Injection.

Women who are living with HIV or are on antiretroviral (ARV) therapy can safely use progestin-only injectables such as Medogen 150 mg/ml Suspension for Injection.

4.2 Posology and method of administration

Medogen 150 mg/ml Suspension for Injection is given intramuscularly every 12 weeks.

First injection

The first dose of Medogen 150 mg/ml Suspension for Injection can be given:

- within 7 days of the start of the woman's monthly bleeding in women who are menstruating
- immediately if switching from an intra-uterine device (IUD)
- immediately if switching from a correctly used hormonal method
- immediately if switching when a repeat injection of another injectable method is due

If more than 7 days have passed since the start of her monthly bleeding, or the woman does not have monthly bleeding, or the woman has not been using another contraception method consistently, she can receive the injection at any time so long as it is reasonably certain she is not pregnant. In such a case she should use an additional (backup) method of contraception for the first 7 days.

First injection after birth

If the woman is *fully breast-feeding*, the first dose of Medogen 150 mg/ml Suspension for Injection can be given:

- any time between 6 weeks and 6 months of birth if her monthly bleeding has not returned
- any time after more than 6 months of birth if her monthly bleeding has not returned and it is reasonably certain she is not pregnant; an additional (backup) method of contraception should be used for the first 7 days
- as for women who are menstruating (see above) if the woman's monthly bleeding has returned

If the woman is *partially breast-feeding*, the first dose of Medogen 150 mg/ml Suspension for Injection can be given:

- 6 weeks after birth
- any time after more than 6 weeks of birth if her monthly bleeding has not returned and it is reasonably certain she is not pregnant; an additional (backup) method of contraception should be used for the first 7 days
- as for women who are menstruating (see above) if the woman's monthly bleeding has returned

If the woman is *not breast-feeding*, the first dose of Medogen 150 mg/ml Suspension for Injection can be given:

- up to 4 weeks after birth
- any time after more than 4 weeks of birth if her monthly bleeding has not returned and it is reasonably certain she is not pregnant; an additional (backup) method of contraception should be used for the first 7 days
- as for women who are menstruating (see above) if the woman's monthly bleeding has returned

First injection after miscarriage or abortion

The first dose of Medogen 150 mg/ml Suspension for Injection can be given:

- within 7 days of first- or second-trimester miscarriage or abortion

- any time after 7 days of first- or second-trimester miscarriage or abortion if it is reasonably certain she is not pregnant; an additional (backup) method of contraception should be used for the first 7 days

The injection may be given up to 2 weeks earlier, that is, after 10 weeks of the previous injection.

Managing Late Injections

As long as it is given within 4 weeks of the due dose, she can receive her next injection. No need for tests, evaluation or a backup method.

A client who is more than 4 weeks late for Medogen 150 mg/ml Suspension for Injection can receive her next injection if it is reasonably certain she is not pregnant. She can receive her next injection if:

– She has not had sex since 2 weeks after the scheduled date of her injection, or

– She has used a backup method or has taken emergency contraceptive pills (ECPs) after any unprotected sex since 2 weeks after the scheduled date of her injection, or

– She is fully or nearly fully breast-feeding and she gave birth less than 6 months ago.

She will need to abstain from sex or use a backup method for the first 7 days after the injection.

Method of administration

Medogen 150 mg/ml Suspension for Injection is given by intramuscular injection into the ventro-gluteal muscle, into the deltoid muscle or into the upper outer aspect of the gluteal muscle. The site is chosen according to the woman's preference. Doses should be given by a syringe with 24 gauge needle size.

4.3 Contraindications

Medogen 150 mg/ml Suspension for Injection must not be used in case the woman:

- has hypersensitivity to medroxyprogesterone acetate or to any of the excipients listed in section 6.1;
- is pregnant
- has hormone-dependent malignancy of breast or genital organs
- has undiagnosed abnormal uterine bleeding
- has a history of severe hepatic disease and liver function tests have not returned to normal
- has significant hypertension (systolic pressure of 160 mmHg or higher, diastolic pressure of 100 mmHg or higher)
- has had diabetes for longer than 20 years or has complications of the disease (circulatory, renal, nervous or ophthalmic)
- has a combination of risk factors (e.g. hypertension, diabetes) for cerebrovascular disease
- has a history of ischemic heart disease (e.g. myocardial infarction) or stroke
- has or has had arterial thrombosis
- has acute deep venous thrombosis or pulmonary embolism
- has systemic lupus erythematosus with positive test for antiphospholipid antibodies or severe thrombocytopenia

4.4 Special warnings and precautions for use

Loss of Bone Mineral Density:

Use of medroxyprogesterone acetate 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 long-term use of medroxyprogesterone acetate; however, BMD appears to increase after medroxyprogesterone acetate 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 growth. It is unknown if use of medroxyprogesterone acetateby younger women will reduce peak bone mass and increase the risk for fracture in later life.

WHO has concluded that the decrease in bone mineral density does not place age or time limits on use of medroxyprogesterone acetate.

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

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

In particular, in women with significant lifestyle or medical risk factors for osteoporosis, other methods of contraception should be considered prior to use of medroxyprogesterone acetate.

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

A retrospective cohort study reported that women using medroxyprogesterone acetate injections (DMPA), have a higher risk of fracture compared with contraceptive users with no recorded use of DMPA (incident rate ratio 1.41, 95% CI 1.35-1.47 for the five year follow-up period); it is not known if this is due to DMPA, or to other related lifestyle factors which have a bearing on fracture rate. By contrast, in women using DMPA, the fracture risk before and after starting DMPA was not increased (relative risk 1.08, 95% CI 0.92-1.26). Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life.

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: DMPA 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 (longer than 10 days) episodes of bleeding (up to 33% of women in the first 3 months of use decreasing to 12% by month 12). Heavy prolonged bleeding may rarely 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 use of oestrogen. This may be either in the form of a low dose (30 micrograms oestrogen) combined oral contraceptive pill or 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 use of oestrogen is not recommended.

Return to Fertility: There is no evidence that DMPA 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.

HIV Acquisition Risk:
Women who are at high risk of HIV infection and use a progestin only injectable are more likely to get HIV. The injectable may or may not be responsible for increasing a woman's chances of becoming infected if exposed to HIV. An expert group convened by WHO concluded, "Women should not be denied the use of progestogen-only injectables because of concerns about the possible increased risk" of HIV infection.

In countries and populations where HIV is common, health care providers should clearly inform women interested in progestin-only injectables how to protect themselves from HIV, so that each woman can make a fully informed choice. Women should be told clearly that they can choose and use a progestin-only injectable if they wish. Women also should be told that other long-acting and effective methods are available if they would like to consider a different method.

Cancer Risks:
DMPA does not cause cancer. DMPA helps protect against cancer of the lining of the uterus (endometrial cancer). Findings of the few studies on DMPA use and breast cancer are similar to findings with combined oral contraceptives: Women using DMPA were more likely to be diagnosed with breast cancer while using DMPA or within 10 years after they stopped. It is unclear whether these findings are explained by earlier detection of existing breast cancers among DMPA users or by a biologic effect of DMPA on breast cancer.

There may be a slightly increased risk of cervical cancer among women using DMPA for 5 years or more. Cervical cancer cannot develop because of DMPA alone, however, it is caused by persistent infection with human papillomavirus.

Weight Gain: There is a tendency for women to gain weight while on DMPA therapy. Studies indicate that over the first 1-2 years of use, average weight gain was 5-8 lbs (2-4 kg). Women completing 4-6 years of therapy gained an average of 14-16.5 lbs (6-8 kg). The weight gained is caused by increased fat and is not secondary to an anabolic effect or fluid retention.

Anaphylaxis: There is a tendency for anaphylactic responses (anaphylactic reactions, anaphylactic shock, anaphylactoid reactions) to occur while on DMPA therapy.

Thrombo-embolic Disorders: If the patient experience pulmonary embolism, cerebrovascular disease or retinal thrombosis while receiving DMPA, the drug should not be given again.

Psychiatric Disorders: Patients with a history of endogenous depression should be carefully monitored. Some patients may complain of premenstrual-type depression while on DMPA 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 health care provider 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 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 DMPA.

A decrease in glucose tolerance has been observed in some patients treated with progestogens. Diabetic patients should therefore be carefully monitored while receiving progestogen therapy.
There have been rare cases of thrombo-embolism with use of DMPA, but causality has not been established.

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

The use of DMPA 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.

Health care providers should carefully consider the use of DMPA in patients with recent trophoblastic disease before levels of human chorionic gonadotrophin have returned to normal.

Health care providers should inform pathologists of the patient's use of DMPA if endometrial or endocervical tissue is submitted for examination.

The results of certain laboratory tests may be affected by the use of DMPA. 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 DMPA 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.

Excipients:
Each vial contains methyl paraben and propyl paraben which may cause allergic reactions (possibly delayed), and exceptionally bronchospasm.

This medicinal product also contains less than 1mmol sodium i.e., is essentially ‘sodium-free’.
It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

The bioavailability of medroxyprogesterone acetate may be significantly depressed when it is administered concurrently with aminoglutethimide.

Interactions with other medicinal treatments (including oral anticoagulants) have rarely been reported, and 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. It is therefore 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 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 medroxyprogesterone acetate have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy

Medogen 150 mg/ml Suspension for Injection 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. If Medogen 150 mg/ml Suspension for Injection is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

One study found that infants from unintentional pregnancies that occurred 1 to 2 months after injection of medroxyprogesterone acetate 150 mg IM were at an increased risk of low birth weight; this, in turn, has been associated with an increased risk of neonatal death. However, the overall risk of this is very low because pregnancies while on medroxyprogesterone acetate Injection 150 mg IM are uncommon.

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

Medroxyprogesterone acetate is excreted in human milk in small amounts. In general, no effects of MPA have been shown in breastfed newborns/infants of treated mothers.

Medogen 150 mg/ml Suspension for Injection can be used during breast-feeding.

Available data are not sufficient to exclude a negative effect of medroxyprogesterone acetate in breastfed infants less than six weeks old. Current recommendations on contraception and breast-feeding should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility

Women may experience a delay in return to fertility (conception) following discontinuation of Medogen 150 mg/ml Suspension for Injection (see section 4.4).

4.7 Effects on ability to drive and use machines

DMPA 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
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)				Breast cancer
Blood & 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, Affective disorder, Irritability, Anxiety
Nervous system disorders	Headache	Dizziness	Seizure, Somnolence, Paraesthesia	Migraine, Paralysis, Syncope
Ear & Labyrinth Disorder				Vertigo
Cardiac disorder				Tachycardia
Vascular disorders			Hot flush	Embolism & thrombosis,

				Deep vein thrombosis, Thrombophlebitis, Hypertension, Varicose veins
Respiratory, thoracic & 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
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 atrophy, 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
Investigation	Weight increased, Weight decreased			Bone density decreased, Glucose tolerance decreased, Cervical smear abnormal

*ADR identified post-marketing

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. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

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 Medogen 150 mg/ml Suspension for Injection with women using medroxyprogesterone acetate injection (150 mg IM) showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the Medogen 150 mg/ml Suspension for Injection group are listed in Table 1.

Table 1. Mean Percent Change from Baseline in BMD in Women Using Medogen 150 mg/ml Suspension for Injection 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)

In another controlled, clinical study adult women using medroxyprogesterone acetate 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. Please refer to Table 2 below for further details.

After stopping use of medroxyprogesterone acetate injection (150 mg 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.

Table 2. Mean Percent Change from Baseline in BMD in Adults by Skeletal Site and Cohort after 5 Years of Therapy with medroxyprogesterone acetate 150 mg IM and after 2 Years Post-Therapy or 7 Years of Observation (Control)

Time in Study	Spine		Total Hip		Femoral Neck	
	Medroxyprogesterone acetate	Control	Medroxyprogesterone acetate	Control	Medroxyprogesterone acetate	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received medroxyprogesterone acetate injection (150 mg 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 medroxyprogesterone acetate Injection (150 mg 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.

BMD Changes in Adolescent Females (12-18 years)

Results from an open-label, non-randomised, clinical study of medroxyprogesterone acetate Injection (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. Post-treatment follow-up showed that, based on mean values, lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued and that hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued. 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 (n=71 at 60 weeks and n=25 at 240 weeks after treatment discontinuation). 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.

5.2 Pharmacokinetic properties

Absorption of Medogen 150 mg/ml Suspension for Injection

The absorption characteristics of Medogen 150 mg/ml Suspension for Injection have been determined after administration of one (1) intramuscular injection in healthy adult female volunteers in the fasting state as follows:

Medroxyprogesterone acetate

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**
Maximum concentration (C_{max})	2299 ± 1051 pg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	3275 ± 774 ng.h/mL
Time to attain maximum concentration (Tmax)	234 ± 545 h

Pharmacokinetics of Medroxyprogesterone acetate

General	
	Medroxyprogesterone acetate has a long duration of action as a result of slow absorption from the injection site.
Absorption	
Oral bioavailability	Not applicable
Distribution	
Volume of distribution (mean)	20±3 L
Plasma proteinbinding*in vitro*	90 to 95%,
Tissue distribution	Medroxyprogesterone acetate binding occurs primarily to serum albumin. It crosses the blood-brain barrier and is secreted in breast milk.
Metabolism	
	The principal metabolite is 6α-methyl-6β, 17α, 21-trihydroxy-4-pregnene-3, 20-dione-17-acetate. At least 11 metabolites have been reported. All are excreted in the urine, some, but not all, conjugated. CYP3A4 is involved in the metabolism.
Active metabolite	None
Elimination	
Elimination half life	≈6 weeks (following i.m administration)
Mean systemic clearance (Cl/F)	1600-4000 L/day
% of dose excreted in urine	NA*
% of dose excreted in faeces	NA*
Metabolizing enzymes	Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on medroxyprogesterone acetate have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

NA*-Not available

Patients with hepatic impairment

The effect of a hepatic impairment on the pharmacokinetics of medroxyprogesterone acetate is unknown. However, medroxyprogesterone acetate is almost exclusively eliminated by hepatic metabolism and metabolism may be reduced in patients with hepatic impairment.

Patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of medroxyprogesterone acetate is unknown.

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.

Medroxyprogestrone acetate has been shown to have adverse effects on reproduction in animal studies. It caused facial clefts in rabbits but not in rats or mice. Genital anomalies, masculinisation of females and feminisation of males have been reported in rats and non-human primates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene glycol 3350, polysorbate 80 (tween 80), sodium chloride (injectable grade), methyl paraben, propyl paraben, sodium hydroxide (for adjustment of pH), hydrochloric acid (for adjustment of pH), nitrogen (injectable grade, for air displacement) and water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze.

Store vials in the cartons to protect from light.

6.5 Nature and contents of container

Type-1 (3mL) clear glass vial, sealed with a 13mm grey chlorobutyl rubber stopper and a red flip–off aluminium seal, containing 1 mL white to off-white suspension. Each filled and sealed glass vial is packed in a printed unit carton.

Pack sizes:

1 vial in an inner carton

20 vials in an inner carton

6.6 Special precautions for disposal and other handling

Shake the vial well just before use in order to obtain homogeneous suspension.

Discard any unused contents in accordance with local requirement.

7. SUPPLIER

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