Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product
TRICLOFEM INJECTION 150mg/ml

2. Qualitative and quantitative composition
Each mL of suspension contains 150mg Medroxyprogesterone acetate

Excipients with known effect:

Each mL also contains:

- Methyl paraben, 1.351mg
- Propyl paraben, 0.147mg
- Sodium chloride (8.582mg) equivalent to 3.38mg (0.15mmol) sodium,

For the full list of excipients, see section 6.1 List of Excipients

3. Pharmaceutical form
Sterile Suspension for injection
White aqueous suspension for injection.

4. Clinical Particulars
4.1 Therapeutic indications
Triclofem is used for long-term contraception in women aged over 18 years. 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).
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.

Triclofem 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 Triclofem long-term (see section 4.4 Special warnings and special precautions for use), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy or lactation, should be considered before giving Triclofem.

Women who are living with HIV or are on antiretroviral (ARV) therapy can safely use progestin-only injectables such as Triclofem.

4.2 Posology and method of administration
Triclofem is given intramuscularly every 12 weeks.

First injection

The first dose of Triclofem 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 Triclofem 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 Triclofem 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 Triclofem 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 Triclofem 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 Triclofem 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

Triclofem 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.

4.3 Contraindications

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

Triclofem should not be used during pregnancy, either for diagnosis or therapy.

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

Triclofem 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, Triclofem 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.

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 (Triclofem) 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, Triclofem 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 Triclofem.

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 Triclofem 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 Triclofem 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 Triclofem 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"

Weight Gain: There is a tendency for women to gain weight while on Triclofem 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 Triclofem, 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 Triclofem 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 Triclofem.
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 Triclofem, 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 Triclofem 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 Triclofem 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 Triclofem if endometrial or endocervical tissue is submitted for examination.
The results of certain laboratory tests may be affected by the use of Triclofem. 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 Triclofem 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 Triclofem 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 Triclofem use should be discontinued.
Excipient information:
As this product contains methylparahydroxybenzoate and propylparahydroxybenzoate, it may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.
Triclofem contains less than 1 mmol sodium (23 mg) per pre-filled syringe or vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglutethimide administered concurrently with Triclofem may significantly depress the bioavailability of Triclofem.
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:
Triclofem is indicated for the prevention of pregnancy.
Women may experience a delay in return to fertility (conception) following discontinuation of Triclofem (see section 4.4).
Pregnancy:
Triclofem is contraindicated in pregnancy.

Doctors should check that patients are not pregnant before initial injection of Triclofem, and also if administration of any subsequent injection is delayed beyond 89 days (12 weeks and five days).
Infants from accidental pregnancies that occur 1-2 months after injection of Triclofem 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 such pregnancies 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 and/or its metabolites are secreted in breast milk Infants exposed to medroxyprogesterone acetate via breast milk have been studied for developmental and behavioural effects to 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, Triclofem 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
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 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
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
Reproductive system and		Vaginal discharge,	Dysfunctional uterine bleeding	Vaginitis, Amenorrhoea, Breast

breast disorders		Breast tenderness, Dys menorrhea, Gen itourinary tract infection	(irregular, increase, decrease, spotting, Galactorrhoea Pelvic pain, Dyspareunia, Suppressed lactation	pain, Metrorrhagia, Menometrorrhagia, Menorrhagia,Vulvovag inal 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		Oedema/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 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 https://pv.pharmacyboardkenya.org

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**	12	60	7	39	13	63

n Mean (SD) 95% CI	-3.1% (3.15) -5.13; -1.13	0.5% (3.65) -0.39; 1.49	-1.3% (4.95) -5.92; 3.23	0.9% (3.81) -0.29; 2.17	-5.4% (2.73) -7.03; -3.73	-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 24 60 120 180 240	98 74 71 52 39 25	9 9 8 10 7 9	-4.1 (0.43) -4.1 (0.53) -3.6 (0.46) -4.3 (0.64) -4.1 (0.72) -3.4 (0.67)	[-4.95; -3.25] [-5.15; -3.04] [-4.48; -2.66] [-5.56; -2.98] [-5.55; -2.63] [-4.73; -1.98]	N/A -4.0 (0.61) -2.8 (0.56) -1.7 (0.72) -1.2 (0.85) 0.1 (0.98)	[-5.25; -2.80] [-3.97; -1.72] [-3.14; -0.26] [-2.96; 0.46] [-1.95; 2.11]
Femoral Neck BMD						
0 24 60 120 180 240	98 74 71 52 39 25	9 9 8 10 7 9	-3.9 (0.50) -3.8 (0.60) -3.3 (0.56) -3.8 (0.74) -3.9 (0.85) -3.4 (0.80)	[-4.92; -2.92] [-5.01; -2.62] [-4.41; -2.18] [-5.25; -2.28] [-5.62; -2.17] [-5.07; -1.78]	N/A -4.0 (0.71) -3.6 (0.70) -1.8 (0.82) -1.0 (0.98) -0.7 (1.19)	[-5.40; -2.55] [-4.99; -2.18] [-3.43; -0.13] [-3.00; 0.97] [-3.20; 1.72]
Lumbar Spine BMD						
0 24 60 120 180 240	98 74 70 52 39 25	9 9 8 10 7 9	-2.7 (0.39) -2.6 (0.43) -2.8 (0.43) -2.7 (0.61) -3.0 (0.67) -2.6 (0.80)	[-3.45; -1.91] [-3.42; -1.69] [-3.66; -1.96] [-3.96; -1.50]	N/A -2.5 (0.51) -0.2 (0.60) 2.2 (0.73) 2.8 (0.79) 4.5 (1.03)	[-3.52; -1.48] [-1.41; 1.01] [0.74; 3.67] [1.16; 4.35]

				[-4.35; -1.66] [-4.28; -0.99]		[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

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. 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

Methylparaben
Propylparaben
Polyethylene Glycol 3350
Sodium Chloride

Polysorbate 80,
Sodium Hydroxide (for adjustment of pH)
Hydrochloric Acid (for adjustment of pH)
Water for injection

6.2 Incompatibilities
Not to be diluted with water.

6.3 Shelf life
60 Months

6.4 Special precautions for storage
Do not store above 30°C.
Keep the glass vial in the provided carton to protect the product from light. Do not freeze. Vials must be stored upright. Avoid excursions above 30°C.

6.5 Nature and contents of container
2mL clear tubular USP type 1 glass vial, closed with a red bromobutyl rubber stopper and a purple flip cap aluminium seal, containing 1 mL white aqueous suspension.
Pack size:
Carton containing 20 vials.

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. Marketing Authorization Holder
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8. Marketing authorization number(s)
CTD10190.

9. Date of first authorization/renewal of the authorization
17/08/2023.

10. Date of revision of the text
14/09/2023

11. Dosimetry
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals
Not Applicable.