SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<TRADE NAME> <STRENGTH> Suspension for Injection

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains <STRENGTH> of medroxyprogesterone acetate.

Excipient with known effect:

<REGARDING THE APPROVAL>

For the full list of excipients, see section 6.1.

1. PHARMACEUTICAL FORM

Sterile Suspension for Injection

<REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   1. Therapeutic indications

Progestogen:

* for long-term female contraception. Each injection prevents ovulation and provides contraception for at least 12 weeks (+/- 5 days). However, it should be taken into consideration that the return to fertility (ovulation) may be delayed for up to one year (see section 4.4).
* for use in women who have been appropriately counselled concerning the likelihood of menstrual disturbance and the potential for a delay in return to full fertility.
* 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 medroxyprogesterone acetate injection long-term (see section 4.4), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered before giving the injection of medroxyprogesterone acetate.

Paediatric population (12-18 years)

In adolescents, medroxyprogesterone acetate injection may be used, but only after other methods of contraception have been discussed with the patient and considered unsuitable or unacceptable.

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

* 1. Posology and method of administration

Posology

*Adults:*

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

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

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

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

Further doses: These should be given at 12 week intervals, however, as long as the injection is given no later than five days after this time, no additional contraceptive measures (e.g. barrier) are required. (N.B. For partners of men undergoing vasectomy, a second injection of 150 mg I.M. 12 weeks after the first may be necessary in a small proportion of patients where the partner's sperm count has not fallen to zero.) If the interval from the preceding injection is greater than 89 days (12 weeks and five days) for any reason, then pregnancy should be excluded before the next injection is given and the patient should use additional contraceptive measures (e.g. barrier) for fourteen days after this subsequent injection.

*Elderly:* Not appropriate.

*Paediatric population:*

Medroxyprogesterone acetate is not indicated before menarche (see section 4.1 Therapeutic Indications).

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

*Switching from other Methods of Contraception*

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

*Hepatic Insufficiency*

The effect of hepatic disease on the pharmacokinetics of medroxy-progesterone acetate is unknown. As medroxyprogesterone acetate largely undergoes hepatic elimination it may be poorly metabolised in patients with severe liver insufficiency (see section 4.3).

*Renal Insufficiency*

The effect of renal disease on the pharmacokinetics of medroxyprogesterone acetate is unknown. No dosage adjustment should be necessary in women with renal insufficiency, since medroxyprogesterone acetate is almost exclusively eliminated by hepatic metabolism.

Method of Administration

The sterile aqueous suspension of medroxyprogesterone acetate should be vigorously shaken just before use to ensure that the dose being given represents a uniform suspension of medroxyprogesterone acetate.

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

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

* 1. Contraindications

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

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

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

Medroxyprogesterone acetate 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, medroxyprogesterone acetate 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.

* 1. 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 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, 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.

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 medroxyprogesterone acetate.

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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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-use | Possible additional cased per 10,000 DMPA users |
| 20 | Less than 1 | Much less than 1 |
| 30 | 44 | 2-3 |
| 40 | 160 | 10 |

\*based on use for 5 years”

*Meningioma:* Meningiomas have been reported following long term administration of progestogens, including medroxyprogesterone acetate. Medroxyprogesterone acetate should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone acetate to patients with a history of meningioma.

*Weight Gain:* There is a tendency for women to gain weight while on medroxyprogesterone acetate 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 medroxyprogesterone acetate, 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate.

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 medroxyprogesterone acetate, 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate if endometrial or endocervical tissue is submitted for examination.

The results of certain laboratory tests may be affected by the use of medroxyprogesterone acetate. 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate use should be discontinued.

Excipient information:

As this product contains methylparahydroxybenzoate and propylparahydroxybenzoate, it may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

Medroxyprogesterone acetate contains less than 1 mmol sodium (23 mg) per pre-filled syringe or vial, that is to say essentially ‘sodium-free’. <REGARDING THE APPROVAL>

* 1. Interaction with other medicinal products and other forms of interaction

Aminoglutethimide administered concurrently with medroxy-progesterone acetate may significantly depress the bioavailability of medroxyprogesterone acetate.

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.

* 1. Fertility, pregnancy and lactation

Fertility

MPA at oral doses may inhibit ovulation.

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

Pregnancy

medroxyprogesterone acetate is contraindicated in women who are pregnant.

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

If medroxyprogesterone acetate is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the foetus.

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

Breast-feeding

Medroxyprogesterone acetate and its metabolites are secreted in breast milk.

In nursing mothers treated with medroxyprogesterone acetate injection 150 mg IM every 3 months, milk composition, quality, and amount are not adversely affected

Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

However, due to limitations of the data regarding the effects of MPA in breastfed infants less than six weeks old, medroxyprogesterone acetate should be given no sooner than six weeks post-partum when the infant’s enzyme system is more developed.

* 1. Effects on ability to drive and use machines

Medroxyprogesterone acetate may cause headaches and dizziness. Patients should be advised not to drive or operate machinery if affected..

* 1. 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 |
| 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 breast disorders |  | Vaginal discharge, Breast tenderness, Dysmenorrhea, Genitourinary tract infection | Dysfunctional uterine bleeding (irregular, increase, decrease, spotting, Galactorrhoea Pelvic pain, Dyspareunia, Suppressed lactation | Vaginitis, Amenorrhoea, Breast pain, Metrorrhagia, Menometrorrhagia, Menorrhagia, Vulvovaginal dryness, Breast atropy, Ovarian cyst, Premenstrual syndrome, Endometrial hyperplasia, Breast mass, Nipple exudate bloody, Vaginal cyst, Breast enlargement, Lack of return to fertility, Sensation of pregnancy |
| General disorders and administration site conditions |  | Odema/Fluid retention, Asthenia | Chest pain | Pyrexia, Fatigue, Injection site reaction\*, Injection site persistent atrophy/indentation/dimpling\*, Injection site nodule/lump\*, Injection site pain/tenderness\* Thirst, Dysphonia, VIIth nerve paralysis, Axillary swelling |
| 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 Health Product Vigilance Center; HPVC

* 1. Overdose

No positive action is required other than cessation of therapy.

1. PHARMACOLOGICAL PROPERTIES
   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 | 100 | -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 on study** | **Spine** | | **Total Hip** | | **Femoral Neck** | |
| DMPA | Control | DMPA | Control | DMPA | Control |
| 5 years\*  n  Mean  (SD)  95% CI | 33  -5.4%  (3.57)  -6.65; -4.11 | 105  0.4%  (3.27)  -0.20; 1.06 | 21  –5.2%  (3.60)  -6.80; -3.52 | 65  0.2%  (3.18)  -0.60; 0.98 | 34  -6.1%  (4.68)  -7.75; -4.49 | 106  -0.3%  (5.22)  -1.27; 0.73 |
| 7 years\*\*  N  Mean  (SD)  95% CI | 12  -3.1%  (3.15)  -5.13; -1.13 | 60  0.5%  (3.65)  -0.39; 1.49 | 7  -1.3%  (4.95)  -5.92; 3.23 | 39  0.9%  (3.81)  -0.29; 2.17 | 13  -5.4%  (2.73)  -7.03; -3.73 | 63  -0.0%  (5.88)  -1.51; 1.45 |

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

\*\* The treatment group consisted of women who received DMPA-IM for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

SD = Standard Deviation

CI = Confidence Interval

*BMD Changes in Adolescent Females (12-18 years)*

Results from an open-label, non-randomised, clinical study of DMPA-IM (150 mg IM every 12 weeks for up to 240 weeks (4.6 years), followed by post–treatment measurements) in adolescent females (12-18 years) also showed that medroxyprogesterone acetate IM use was associated with a significant decline in BMD from baseline. Among subjects who received 4 injections/60-week period, the mean decrease in lumbar spine BMD was - 2.1 % after 240 weeks (4.6 years); mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. Please refer to table 3. In contrast, a non-comparable cohort of unmatched, untreated subjects, with different baseline bone parameters from the DMPA users, showed mean BMD increases at 240 weeks of 6.4%, 1.7% and 1.9% for lumbar spine, total hip and femoral neck, respectively.

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

|  |  |  |
| --- | --- | --- |
| **Duration of Treatment** | **DMPA-IM** | |
| **N** | **Mean % Change [95% CI]** |
| Total Hip BMD  Week 60 (1.2 years)  Week 120 (2.3 years)  Week 180 (3.5 years)  Week 240 (4.6 years) | 113  73  45  28 | -2.7 [-3.27; -2.12]  -5.4 [-6.16; -4.64]  -6.4 [-7.38; -5.37]  -6.4 [-8.56; -4.24] |
| Femoral Neck BMD  Week 60  Week 120  Week 180  Week 240 | 113  73  45  28 | -2.9 [-3.72; -2.15]  -5.3 [-6.23; -4.37]  -6.0 [-7.31; -4.59]  -5.4 [-7.81; -3.00] |
| **Lumbar Spine BMD**  Week 60  Week 120  Week 180  Week 240 | 114  73  44  27 | -2.5 [-2.95; -1.98]  -2.7 [-3.57; -1.91]  -2.7 [-3.99; -1.35]  -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]  [ -4.35; -1.66]  [ -4.28; -0.99] | 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]  [ 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.

* 1. 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.

* 1. Preclinical safety data

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

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

Not applicable.

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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