Depo-Provera®

150 mg suspension for injection

Medroxyprogesterone acetate

PAA157405
075

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEPO-PROVERA 150 mg suspension for injection

Medroxyprogesterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is medroxyprogesterone acetate.

DEPO-PROVERA suspension for injection contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Suppression of ovulation (contraception).

It should be considered that the return to fertility (ovulation) may be delayed for up to one year after discontinuation of DEPO-PROVERA (see section 4.4).

Since loss of bone mineral density may occur in females of all ages who use DMPA long-term (see section 4.4 Special warnings and precautions for use), a risk/benefit assessment, which also takes into consideration the decrease in bone mineral density (BMD) that occurs during pregnancy and/or lactation, should be considered.

4.2 Posology and method of administration

The recommended dose for the suppression of ovulation is 150 mg every three months, administered by deep, intramuscular injection into the gluteal or deltoid muscle. To increase assurance that the patient is not pregnant at the time of the first administration, this injection should be given during the first 5 days following a normal menstrual period; in the first 5 days postpartum if the patient is not breast-feeding; if the patient is breast-feeding, at or after 6 weeks postpartum. If the interval between the injections is greater than 13 weeks, physician should ensure that the patient is not pregnant before administering the product.
Doctors are recommended to warn the patient at the beginning of treatment that her menstrual cycle may be disturbed, that irregular unpredictable bleeding or spotting may occur but that this will diminish as treatment with DEPO-PROVERA is continued and will finally result in amenorrhoea.
Excessive or prolonged bleeding which becomes a nuisance to the patient can generally be controlled by oral or parenteral administration of oestrogens, namely 0.05 to 0.1 mg of ethinyl estradiol per day for 7 to 21 days. This treatment may be continued for 1 to 2 cycles, but should not be considered as a long-term treatment. Based on limited experience, some investigators are in favour of giving a second injection of DEPO-PROVERA before 90 days, to control annoying bleeding. Following injections are administered at 90-day intervals. If abnormal bleeding persists, appropriate examinations should be performed to exclude the possibility of a pathological condition.

Switching from other methods of contraception to DEPO-PROVERA: When switching from other contraceptive methods to DEPO-PROVERA, the latter should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives to DEPO-PROVERA should have their first injection of DEPO-PROVERA within 7 days after taking their last active pill).

Hepatic Insufficiency: No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of medroxyprogesterone acetate. However, medroxyprogesterone acetate is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see section 4.3).

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

Paediatric population:
DMPA-IM is not indicated before menarche (see section 4.1 Therapeutic indications).

Data in adolescent females (12-18 years) is available for IM administration of MPA (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA is expected to be the same for adolescents after menarche and adult females.

4.3 Contraindications

The use of DEPO-PROVERA is contraindicated in the event of:
- hypersensitivity to medroxyprogesterone acetate or to any of the excipients listed in section 6.1.
- undiagnosed vaginal bleeding
- undiagnosed bleeding of the urinary tract
- diagnosed or suspected breast cancer
- active thrombophlebitis or a history of thromboembolism or cerebrovascular disease. Physicians should be alert to the manifestation of the first symptoms (thrombophlebitis, pulmonary embolism, cerebrovascular disease and retinal thrombosis)
- pregnancy or suspected pregnancy
- severe hepatic impairment or hepatic function disorders

4.4 Special warnings and precautions for use

Loss of Bone Mineral Density
Use of 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 DEPO-PROVERA 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 intramuscular injection 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, DEPO-PROVERA may be used but only after other methods of contraception have been discussed with the patients and considered to be unsuitable or unacceptable.

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

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years. In particular, in women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered prior to use of DEPO-PROVERA. Significant risk factors for osteoporosis include:
- Alcohol abuse and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- Low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- Previous low trauma fracture
- Family history of osteoporosis

For further information on BMD changes in both adult and adolescent females, refer to section 5.1. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Breast cancer:
The use of combined oral oestrogens and progestins by post-menopausal women has been reported to increase the risk of breast cancer. Results from a randomized placebo-controlled trial, the WHI (Women's Health Initiative) trial, and epidemiological studies have indicated an increased risk of breast cancer in women taking oestrogens/progestins combinations for hormone therapy for several years. In the WHI trial on the combined use of conjugated equine oestrogens (CEE) and medroxyprogesterone acetate and in the observation studies, the excess risk increased with duration of use (see section 4.2). The combined use of oestrogens and progestins has also been reported to result in an increase in abnormal mammograms requiring further evaluation.

In several epidemiological studies, no overall increased risk for breast cancer was found among women using long-acting injectable (depot) progestins compared with women not using them. However, an increased relative risk (e.g. 2.0 in one study) was found for women who currently used long-acting injectable progestins or had used them only a few years before. It is not possible to infer from these data whether this increased rate of breast cancer diagnosis among women using currently long-acting injectable progestins was due to increased surveillance among these women, to the biological effects of these injectable progestins or to a combination of reasons**.**
In case-control studies, long-term monitoring of DEPO-PROVERA users has shown a slight increase or no increase in the overall risk of breast cancer and no increase in the overall risk of ovarian, cervical or liver cancer and has demonstrated the prolonged protective effect of a reduction in the risk of endometrial cancer in the user population. An increased relative risk of 2.19% (95% CI of 1.23 to 3.89) of breast cancer has been associated with taking DEPO-PROVERA in women of less than 35 years old exposed to the drug for the first time in the 4 previous years. However, the overall relative risk for those who had used it over a long period was only 1.2% (95% CI of 0.96 to 1.52). Other recent analyses have shown similar results.

Before beginning treatment with DEPO-PROVERA, the patient must undergo a thorough general examination during which any genital or mammary neoplasia must be excluded. This examination must be repeated each year. This precaution does not concern patients in whom the treatment has been initiated for recurrent cancer of the endometrium, breast or kidneys.

Medroxyprogesterone acetate has not been causally associated with the induction of thrombotic or thromboembolic disorders, however medroxyprogesterone acetate is not recommended in any patient with a history of venous thromboembolism. Discontinuation of medroxyprogesterone acetate is recommended in patients who develop venous thromboembolism while undergoing therapy with medroxyprogesterone acetate.

DEPO-PROVERA exerts a prolonged contraceptive effect. The mean time to conception for women who conceive is 10 months after the last injection, the range being from 4 to 31 months, and is not linked to the time during which the contraceptive has been used.

In the event of sudden onset of full or partial loss of vision or if proptosis, diplopia or migraine appears, DEPO-PROVERA should not be re-administered before an examination is undertaken. DEPO-PROVERA must be discontinued if the findings should reveal papilloedema or damage to the vessels of the retina.

DEPO-PROVERA can cause weight gain and fluid retention. Caution must be exercised with patients suffering from conditions that could be negatively affected by these factors.

Most women using DEPO-PROVERA present a pattern of disturbed menstrual bleeding, which may include irregular or unpredictable bleeding or spotting, or more rarely heavy or continuous bleeding. As treatment continues, fewer patients suffer irregular bleeding and more have amenorrhoea. In the case of breakthrough bleeding, as in all cases of irregular vaginal bleeding, organic causes must be considered. Any unexpected vaginal bleeding during the treatment with DEPO-PROVERA must be investigated. Routine or long-term cyclic use of additional oestrogens to control abundant or prolonged bleeding while using DEPO-PROVERA as a means of contraception is not recommended.

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.

Protection against Sexually Transmitted Infections
Women should be counselled that DEPO-PROVERA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. 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.

A decrease in glucose tolerance has been observed in some patients receiving progestin treatment. Diabetic patients treated with progestin should be closely monitored and antidiabetic treatment must be possibly adapted.

If jaundice develops, interrupting the treatment must be considered.

Anatomical pathologists should be informed of the treatment with DEPO-PROVERA whenever they are given endometrial and endocervical tissue samples for analysis.

The physician/laboratory must be informed of the fact that the use of DEPO-PROVERA can lower the levels of the following endocrine biological markers:
a. Plasma/urinary steroids (e.g. cortisol, oestrogen, pregnandiol, progesterone, testosterone)
b. Plasma/urinary gonadotrophins (e.g. luteinising hormone and follicle stimulating hormone)
c. Sex-hormone-binding globulin

Since this product contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, it could cause allergic reactions (possibly delayed), and exceptionally bronchospasm.

4.5 Interactions with other medicinal products and other forms of interaction

Aminoglutethimide administered concomitantly with high-dose medroxyprogesterone acetate may significantly depress the bioavailability of medroxyprogesterone acetate. Patients using high-dose medroxyprogesterone acetate should be warned of the possibility of decreased efficacy with the use of aminoglutethimide.

For interactions with certain laboratory tests, see the last paragraph of the previous section (4.4)

4.6 Fertility, pregnancy and lactation

Fertility
Medroxyprogesterone acetate suppresses the ovulation. At contraceptive doses, the ovulation returns in general 13 months after end of treatment (see section 4.2)

Pregnancy
Medroxyprogesterone acetate is contra-indicated in pregnant women (see section 4.3).

Animal studies have confirmed the reproductive toxicity. Medroxyprogesterone acetate was teratogenic in rabbits, but not in rats when it was administered as a single IM injection during pregnancy (see section 5.3).

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

Children born from unexpected pregnancies occurring one to two months following injection of DEPO-PROVERA may have a high risk of low birth weight, which is in turn associated with a higher risk of neonatal death.
The supposed risk is low because such pregnancies are uncommon.

The use of progestins is not recommended for establishing a diagnosis of pregnancy.

Patients using medroxyprogesterone acetate during pregnancy or becoming pregnant during the treatment must be warned of the potential danger to the foetus.

Breast-feeding
Medroxyprogesterone acetate and its metabolites are excreted in human milk. There is no evidence to indicate that this involves any risk for the child.
However, it is recommended to not administer DEPO-PROVERA before 6 weeks post-partum to reduce the exposure of the newborn.

4.7 Effects on ability to drive and use machines

There are no known data regarding the effect on the ability to drive or operate machinery. In view of the pharmacological profile of medroxyprogesterone acetate no significant effect should be expected.

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%).

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	Frequency not known (cannot be estimated from the available data)
Immune system disorders			Drug hypersensitivity		Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Endocrine disorders					Prolonged anovulation, Moon face
Psychiatric disorders	Nervousness	Depression, Reduced libido	Insomnia		Absence of orgasm
Nervous system disorders	Headache	Dizziness	Convulsions, Somnolence		
Vascular disorders			Hot flushes	Embolism and thrombosis, thrombophlebitis	
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort	Nausea, Abdominal distension			
Hepatobiliary disorders			Hepatic function disorders	Jaundice	
Skin and subcutaneous tissue disorders		Alopecia, Acne, Rash	Hirsutism, Urticaria Pruritus		Lipodystrophy acquired*
Musculoskeletal and connective tissue disorders		Back pain			Arthralgia, Muscle spasms, Osteoporosis, Osteoporotic fractures
Reproductive system and breast disorders		Cervical discharge, Breast tenderness,	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Galactorrhoea, Pelvic pain		Vaginitis, Amenorrhoea, Breast pain
Respiratory, thoracic and mediastinal disorders					Pulmonary embolism
General disorders and administration site conditions		Fluid retention, Asthenia		Pyrexia, Injection site pain/ tenderness*	Fatigue, Injection site reaction*, Injection site persistent atrophy/ indentation/dimpling*, Injection site nodule/ lump*
Investigations	Weight increased, Weight decreased				Glucose tolerance decreased, Loss of bone mineral density
*Adverse Drug Reaction identified post-marketing					

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing 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 according to their local country requirements

4.9 Overdose

Medroxyprogesterone acetate has been very well tolerated. In the case of overdose, nausea and vomiting may occur. Withdrawal bleeding is possible.

5. PHARMACOLOGICAL PROPERTIES

Medroxyprogesterone acetate (17-alpha-hydroxyl-6-alpha-methylprogesterone acetate) is a progesterone derivative.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestin. ATC code: G03AC06

After IM injection, DEPO-PROVERA has a long-lasting progestin action.
Medroxyprogesterone acetate is a progestational agent devoid of androgenic and estrogenic activity.
DEPO-PROVERA suppresses the secretion of pituitary gonadotrophins which, in turn, prevents follicular maturation and ovulation and causes thickening of cervical mucus which inhibits sperm entry into the uterus in women of childbearing potential. This action may also account for the ability of DEPO-PROVERA to ameliorate vasomotor symptoms in the menopausal woman. In male patients, adequate doses of DEPO-PROVERA suppress the Leydig cell function (i.e. suppress the endogenous testosterone production).
Medroxyprogesterone acetate also induces specific progestational changes in the cervical mucus:

- prevents ferning
- increases the viscosity, thus rendering sperm penetration more difficult.

The maturation index in the vaginal epithelium (increase in the intermediate cell count) also changes.
The efficacy of DEPO-PROVERA at pharmacological doses in cancer is probably linked with its activity on the hypothalamic-pituitary-gonad axis and the oestrogen receptors as well as with the steroids metabolism at tissue level.
Like progesterone, medroxyprogesterone acetate is thermogenic.
No suppression of adrenocortical activity has been observed at clinical level at the doses used to inhibit ovulation. However, at very high doses (500 mg or more per day), as used in certain types of cancer, the drug can demonstrate a corticoid-like activity.

BMD Changes in Adult Women
A study comparing changes in BMD in women using DMPA-SC 104 mg with women using DMPA-IM showed similar BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the DMPA-SC group are listed in Table 1.

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

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

CI = Confidence Interval

In another controlled, clinical study, adult women using DMPA-IM for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 2 below for further details.

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

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

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

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

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

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

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

CI = Confidence Interval

Post-treatment follow-up of adolescent participants from the same study, who received at least 1 DMPA injection and provided at least 1 follow-up BMD measurement after stopping DMPA-IM use is shown in Table 4. The median number of injections received in this cohort during the treatment phase was 9. At the time of the final DMPA injection, BMD % changes from baseline in this cohort were -2.7%, -4.1% and -3.9% at the spine, total hip and femoral neck, respectively. Over time, these mean BMD deficits recovered to baseline after DMPA-IM was discontinued. Recovery to baseline required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck. However, it is important to note that a large number of subjects discontinued from the study, therefore these results are based on a small number of subjects and some subjects still had deficit in total hip BMD after 240 weeks. Longer duration of treatment and smoking were associated with slower recovery. Please refer to Table 4 below.

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

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

SE = Standard Error
CI = Confidence Interval

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

Following intramuscular administration, medroxyprogesterone acetate is slowly released, resulting in low, but persistent blood levels. Time to serum peak is approximately 4 to 20 days following an intramuscular dose. Medroxyprogesterone acetate can still be detected in blood for as long as seven to nine months following intramuscular injection.
Medroxyprogesterone acetate is approximately 90 to 95% protein bound. Its distribution volume is 20 ± 3 litres. Medroxyprogesterone acetate crosses the blood-brain-barrier and is excreted in breast milk.
Numerous metabolites of medroxyprogesterone acetate have been described, although not clearly quantified.
The drug's half life after intramuscular administration is 6 weeks.
Medroxyprogesterone acetate is primarily excreted in the faeces, via biliary secretion. Approximately 44% of the drug is excreted unchanged in urine.

5.3 Preclinical safety data

Medroxyprogesterone acetate toxicity has been well defined in the species used in non-clinical studies and is, in general, as expected with progestins, associated with effects on the endocrine and reproductive system.

Medroxyprogesterone acetate was teratogenic in rabbits, but not in rats when it was administered as a single intramuscular injection during pregnancy. The effects observed in rabbits included palatal groove and a dose-dependent increase of dead kittens and non-viable kittens per gestation. Weaker average weights were observed among the young of the two species. Modifications of external genital organs have been observed in the offspring of baboons or cynomolgus monkeys when medroxyprogesterone acetate was administered during pregnancy.

Genotoxicology tests performed in mammals and non-mammals did not show any potential genotoxicity. Prolonged administration of high doses of medroxyprogesterone acetate has induced breast tumours in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350, polysorbate 80, sodium chloride, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), water for injections, hydrochloric acid and/or sodium hydroxide for the pH adjustment.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use Depo Provera after the expiry date which is stated on the Carton/Vial after EXP: The expiry date refers to the last day of that month.

6.4 Special precautions for storage

DEPO-PROVERA 150 mg suspension for injection (1 ml pre-filled syringe):
- Store below 30°C

DEPO-PROVERA 150 mg suspension for injection (1 ml vial):
- Store below 30°C
- Store the vial in a vertical position

6.5 Nature and contents of container

Sterile aqueous suspension for intramuscular injection.

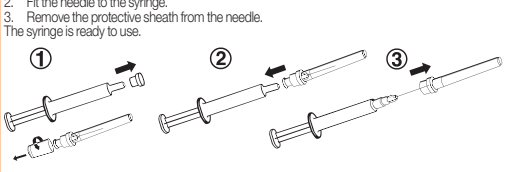
Presentations:
DEPO-PROVERA 150 mg suspension for injection:
- 1 ml pre-filled syringe
- 1 x 1 ml vial, 25 x 1 ml vial

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children
Vial: shake well just before use in order to obtain homogeneous suspension.
Pre-filled syringe: shake well just before use in order to obtain homogeneous suspension.
1. Remove the protective cap.
2. Fit the needle to the syringe.
3. Remove the protective sheath from the needle.

The syringe is ready to use.



After use, the syringe cannot be reused and must be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. FURTHER INFORMATION

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8. DATE OF REVISION OF THE TEXT

March 2020