SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Depo-Provera, 150 mg/mL suspension for injection
Depo-Provera, 150 mg/mL suspension for injection, in prefilled syringe.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL suspension for injection contains 150 mg medroxyprogesterone acetate.

Excipients with known effect:
Methyl parahydroxybenzoate (E 281), propyl parahydroxybenzoate (E 216).
For the full list of excipients, see section 6.1.
Depo-Provera suspension for injection has a pH of 3-7.

3 PHARMACEUTICAL FORM

Suspension for injection, suspension.
Suspension for injection, suspension in prefilled syringe.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Contraception, for women in whom a slow return of fertility after the end of treatment can be accepted. Due to the effect on bone mineral content (see section 4.4), Depo-Provera should only be prescribed to young (< 18 years) women when other methods of contraception are inappropriate. It should be noted, however, that it can take up to one year before fertility (ovulation) is restored (see section 4.4).

- Supplementary treatment in cases of endometrial cancer and endometrioid ovarian cancer. Inoperable breast cancer. Distant metastatic endometrial cancer, as the sole treatment if surgical or radiological treatment has failed. Relief of symptoms in endometriosis.

- Other conditions in which a long-term progestogenic effect without androgenic or oestrogenic side effects is desired.

Since loss of bone mineral density (BMD) may occur in women of all ages who use medroxyprogesterone acetate (MPA) injections long-term (see section 4.4), a risk/benefit assessment should be performed. This assessment should also take into consideration the decrease in bone mineral density that naturally occurs during pregnancy and/or lactation.

4.2 Posology and method of administration

Posology

Contraception: 150 mg every three months. The first injection should be given during the first 3 days of a menstrual period or, in women not nursing, not later than 3 weeks post-partum. In nursing women, the first injection should be given not earlier than 6 weeks post-partum.

Paediatric population
Use of Depo-Provera is not indicated before menarche (see section 4.1). Data are available for use in adolescent females (12-18 years) (see sections 4.4 and 5.1). Apart from concerns regarding the effect on bone mineral content, the safety and effectiveness of Depo-Provera are similar for postmenarcheal adolescent and adult females.

Breast cancer: 500 mg (3.3 mL, 150 mg/mL) per day for 4 weeks (loading dose), then 1,000 mg per week as maintenance therapy. This dose may be divided into 500 mg twice per week. The maintenance therapy should be continued for as long as the tumour responds to treatment.

Endometrial cancer: 1,000 mg (6.7 mL, 150 mg/mL) per week; the treatment is continued for life. After a year or more of lasting remission the dose may be reduced to 500 mg per week.

Relief of symptoms in endometriosis: 100 mg every other week for at least 6 months.

Treatment control

Contraception: Menstrual disturbances such as irregular bleedings and oligomenorrhoea should be investigated before the preparation is prescribed.
Initially, Depo-Provera usually causes irregular bleeding at unpredictable intervals. The lowest number of days of bleeding is achieved if the first injection is given on the 1st or 2nd day of menstruation. If, despite this, the bleedings are troublesome, an improvement can be achieved if the next injection of Depo-Provera is given after an interval shorter than 3 months. Even without such action, the number of days of bleeding diminishes with increasing numbers of injections given at the normal three month intervals. After a year of use, 25-50% of women are entirely without bleedings.
Organic causes should be excluded if break-through bleeding occurs during treatment in patients who were previously amenorrhoeic. Cyclic supplementation of oestrogen in order to control bleeding disturbances during Depo-Provera treatment is *not* recommended.

Method of administration

The suspension must be shaken well and administered in a deep intramuscular injection. Since Depo-Provera is secreted much more slowly from fatty tissue, it is essential that the preparation be injected deep in a muscle.

4.3 Contraindications

- Known or suspected pregnancy.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Depo-Provera should not be given to patients with vaginal bleeding of unknown cause.

Caution should be exercised in cases of hepatic disease and in cases of previous gestational diabetes, and in treatment of women who previously experienced depressed mood during treatment with gestagens or combined oral contraceptives.

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 immediately after initiating the treatment.

Some blood tests may be affected, e.g. liver values may be elevated.

Intake of herbal preparations containing extract of St John's wort (*Hypericum perforatum*) is not recommended while taking Depo-Provera due to the risk of decreased plasma concentrations and reduced clinical effects of Depo-Provera (see section 4.5).

Contraception

The risk of breast cancer generally increases with increasing age. Compared with the risk of developing breast cancer at some point in life, the increased risk associated with oral contraceptive use is minor. The limited information available indicates that the risk associated with oral contraceptives may also be attributable to Depo-Provera. During oral contraceptive treatment, the risk of breast cancer being diagnosed is somewhat increased. The expected number of breast cancer cases/10,000 at different ages, for women using oral contraception and for women who have never used oral contraception, has been calculated as being 4.5/4 (16-19 years), 17.5/16 (20-24 years), 48.7/44 (25-29 years), 110/100 (30-34 years), 180/160 (35-39 years) and 260/230 (40-44 years). The increased risk of breast cancer gradually disappears within 10 years after the end of treatment with oral contraception, and is not related to the duration of treatment, but to the woman's age. The cases of breast cancer that are detected in oral contraceptive users tend to be less advanced than in those who have not used oral contraception. The limited information that is available suggests that this may also apply to Depo-Provera.

After a year of use, 25-50% of the women experience amenorrhoea. With the preparation's high contraceptive effect, the patient can be assured that amenorrhoea is *not* a sign of pregnancy, provided that Depo-Provera was administered regularly in accordance with dosage instructions.

After the end of Depo-Provera treatment, periods of amenorrhoea and infertility persist on average for 6-8 months (in some cases for up to 18 months) as a result of the preparation's depot effect.

Sexually transmitted infections

All women should be counselled that Depo-Provera does not protect against sexually transmitted infections (STIs), e.g. HIV infection (AIDS). Correct and consistent use of condoms reduces the transmission of STIs through sexual contact, including HIV. The benefits of contraceptive options and their risks must be evaluated individually for each woman.

Loss of bone mineral density (BMD)

Use of Depo-Provera reduces serum oestrogen levels in premenopausal women and is associated with a statistically significant loss of bone mineral density due to the known effects of oestrogen deficiency on bone metabolism. Bone loss increases with the length of treatment. Bone mineral content increases, however, following discontinuation of Depo-Provera once ovarian oestrogen production increases.

A loss of bone density is especially concerning during adolescence and early adult age, which are critical periods for bone development. It is not known whether the use of Depo-Provera in younger women reduces the peak bone mass and may thereby increase the risk of fracture later in life, i.e. after menopause.

A study to assess the effects on bone mineral density of Depo-Provera in adolescent females showed that its use was associated with a statistically significant decline in bone mineral density from baseline. After discontinuing Depo-Provera injection in adolescent women, full recovery of bone mineral density required 1.2 years at the lumbar spine, 4.6 years at the hip and 4.6 years at the femoral neck

(see section 5.1**)**. However, in some participants, bone mineral density did not fully recover during the follow-up period; hence the long-term outcome is not known in this group. Depo-Provera should only be prescribed to young (< 18 years) women when other methods of contraception are inappropriate.

A larger observational study of primarily adult female contraceptive users showed that use of Depo-Provera injection had no effect on a woman's risk for fractures. Importantly, this study could not determine whether use of Depo-Provera injections has an effect on fracture rate later in life (see section 5.1 – Relationship of fracture incidence to use of Depo-Provera injections IM (150 mg) in women of reproductive age).

In women of all ages, a risk/benefit assessment should be regularly performed when using Depo-Provera. Other contraceptive methods or endometrial treatments should also be considered, particularly in women with lifestyle and/or other risk factors for osteoporosis.

Examples of risk factors:
- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g. anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis

It is recommended that all patients have adequate calcium and Vitamin D intake.

If the patient has any of the conditions/risk factors that are stated above, the benefit of Depo-Provera for each individual woman must be weighed against the potential risks and discussed with the woman before she decides whether to start the treatment. If any of these conditions or risk factors exacerbate, flare up or appear for the first time, the woman must contact the doctor. The doctor must then decide on potential discontinuation of Depo-Provera.

Oncology use:
Decrease in bone mineral density
Decreases in serum oestrogen due to MPA may result in a decrease in bone mineral density in pre-menopausal women, and may increase the risk for developing osteoporosis later in life. (See "Loss of bone mineral density" above.) There are currently no studies on the bone mineral density effects of the high doses of parenteral MPA (e.g. for oncology use).

Excipients
Depo-Provera contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which may cause allergic reaction (possibly delayed) and in rare cases, bronchospasm.

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Strong enzyme inducing drugs, such as phenobarbital, phenytoin, carbamazepine, rifampicin, rifabutin and primidone, increase the metabolism of gestagens.

Herbal preparations containing St John's wort (*Hypericum perforatum*) can reduce the efficacy of oral contraceptives due to induction of drug metabolising enzymes. This inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort. The corresponding effect on the efficacy of Depo-Provera has not been studied. The consequences of an enzyme induction may be less with the non-oral route. However, until studies are available, it is not recommended that herbal medicines containing St John's wort extract be taken during ongoing contraceptive treatment with

Depo-Provera, as this could potentially lead to a loss of contraceptive effect. Breakthrough bleeding and unintended pregnancies have been reported during co-administration of St John's wort and oral contraceptives.

Medroxyprogesterone acetate (MPA) is metabolized *in vitro* primarily by hydroxylation via CYP3A4. Specific interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted. The plasma concentrations of MPA can be expected to be affected when combined with substances of that type.

4.6 Fertility, pregnancy and lactation

Pregnancy
Depo-Provera should not be administered during pregnancy. If pregnancy should occur during the treatment with Depo-Provera, the treatment must be discontinued at once.

Breast-feeding
Medroxyprogesterone passes into breast milk, but a risk of an effect on the infant appears unlikely with therapeutic doses.

4.7 Effects on ability to drive and use machines

Depo-Provera has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects are presented in the tables below in order of frequency according to the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), not known (cannot be estimated from the available data).

Contraception
The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 4,200 women who received DMPA for contraception for up to 7 years. Those most frequently (> 5%) reported adverse drug reactions were weight increase (69%), headache (16%), nervousness (11%), abdominal pain or discomfort (11%), and decrease in libido (6%).

Initially, medroxyprogesterone usually causes irregular bleedings at unpredictable intervals.

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Immune system disorders				Anaphylactic reactions
Psychiatric disorders		Depression, decreased libido	Increased libido, insomnia	Anxiety
Nervous system disorders	Headache			
Gastrointestinal disorders	Abdominal pain, abdominal discomfort	Nausea		

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Skin and subcutaneous tissue disorders		Acne, alopecia, rash		Acquired lipodystrophy*
Musculoskeletal and connective tissue disorders		Back pain		Pain in extremities, arthralgia
Reproductive system and breast disorders		Breast tenderness	Dysfunctional vaginal bleeding (irregular, increased, decreased, spotting)	Amenorrhoea
General disorders and administration site conditions		Asthenia		Pyrexia, injection site reaction*, injection site pain/tenderness*, persistent atrophy/indentation/dimpling at injection site*, nodule/lump at injection site*
Investigations	Weight increase			
* ADR identified post-marketing				

Oncology

System Organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Endocrine disorders		Moon face		
Metabolism and nutrition disorders	Weight increase			
Nervous system disorders	Tremor			
Vascular disorders		Thrombophlebitis		
Hepatobiliary disorders				
Skin and subcutaneous tissue disorders	Hyperhidrosis			Acquired lipodystrophy *

System Organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Musculoskeletal and connective tissue disorders				Osteoporosis including osteoporotic fractures [#]
Reproductive system and breast disorders		Dysfunctional vaginal bleeding (irregular, increased, decreased, spotting)		
General disorders and administration site conditions	Injection site reaction*, oedema/fluid retention	Injection site pain/tenderness*	Pyrexia	Persistent atrophy/indentation/dimpling at injection site*, nodule/lump at injection site*
Investigations				Abnormal liver values
[#] in patients receiving IM injections of MPA * 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:

Läkemedelsverket
PO Box 26
751 03 Uppsala, Sweden
www.lakemedelsverket.se

4.9 Overdose

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones, progestogens, ATC code: G03DA02, G03AC06

Contraception:
Depo-Provera has a contraceptive effect, predominantly by inhibiting ripening of the follicle in the ovaries, and thus ovulation, and also as a result of the viscosity of the cervical secretion being increased, which inhibits sperm entry into the uterus. Reliability is high, and well comparable with combination-type oral contraceptives - Pearl index approx. 0.2.

The inhibition of ovulation ceases if the concentration of medroxyprogesterone in the blood falls below the therapeutic level. There is no connection between the duration of treatment and the time of return of ovulation.

Cancer:
The mechanism of action of medroxyprogesterone acetate (MPA) is not fully understood. However, experimental data support the theory that the inhibitory effect on breast cancer is related to inhibition of oestrogen receptor synthesis. The frequency of response is correlated to the quantitative occurrence of progesterone and oestrogen receptors. An inhibition of DNA synthesis in human breast cancer cells or in vitro has also been observed with high progesterone concentrations.

After injection of 100-200 mg MPA, transformation of the endometrium from glandular cystic hyperplasia to a picture of early secretion phase could be detected after 7 days, marked glycogen storage in the cells after 33 days, and regressive glandular pictures with decidua-converted stroma after 60 days. After 6 months of continuous treatment with Depo-Provera in a dose of 50 mg/week, the endometrium displayed a picture of the marked atrophic type. Atrophic transformation takes place more rapidly with higher doses of MPA.

Many clinical and experimental indices strongly suggest that Depo-Provera in high doses has a direct effect on cancer cells. This is exploited in order to treat carcinoma in the breasts, ovaries and endometrium. When repeated high-dose injections are given, a gradually increasing serum concentration is obtained (addition), due to more and more intramuscular injection depots being obtained. In order to obtain an adequate serum concentration rapidly, daily injections are given (loading dose). The serum concentration reached is then maintained by 1-2 intramuscular injections per week.

A clinical effect of hormone therapy with Depo-Provera may be expected after 8-10 weeks.

Bone mineral density changes in adult women
In a study to compare the change in BMD in women who used DMPA subcutaneously (DMPA SC) with women who used Depo-Provera DMPA intramuscularly (DMPA IM), an analogous reduction in BMD was observed in the two groups after two years of treatment. The mean percentage change in BMD in the DMPA SC group is reported in table 1.

Table 1. Mean percentage change in BMD (95% confidence interval) from baseline in adult women who used DMPA SC, per skeletal structure

	Lumbar spine		**Hip**		**Femoral neck**	
Treatment length	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 years	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 who used DMPA intramuscularly (DMPA IM) for up to 5 years showed reduced BMD in the spine and hip by 5-6%, while no significant BMD changes were seen in the control group. The reduction in BMD was more pronounced during the first two years, with minor exacerbation during the subsequent years. Mean changes in BMD in the lumbar spine by -2.9% after one year, -4.1% after two years, -4.9% after three years, -4.9% after four years and -5.4% after 5 years, were observed. Mean changes in reduction in BMD of the hip and femoral neck were similar. Further information is given in table 2 below.

After interruption in the use of DMPA IM, the BMD values increased against the baseline value following the treatment period. A longer treatment time was associated with a slower recovery of BMD.

Bone mineral density recovery post-treatment in adult women
In the same study, a range of women were followed after 5 years of treatment with DMPA injections (150 mg IM), for the following two years after the end of treatment. Two years after the end of DMPA injections, BMD increased, and approached baseline levels. Two years after the end of DMPA injections, mean BMD increased in the three skeletal sections, however reduction was assumed to continue: -3.1%, -1.3% and -5.4% at the lumbar spine, hip and femoral neck, respectively. Over the same time interval, women in the control group showed mean changes from baseline of - 0.5%, 0.9% and -0.1% in the lumbar spine, hip and femoral neck, respectively.

Table 2. Average percentage change in BMD (95% confidence interval) from the baseline in adults, per skeletal structure and cohort after five years of treatment with DMPA IM and two years after treatment or after seven years of observation (control)

Length of study	**Spine**		**Hip**		**Femoral neck**	
	DMPA	Control	DMPA	Control	DMPA	Control
5 year*****						
n	33	105	21	65	34	106
Median	-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 year**						
n	12	60	7	39	13	63
Median	-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 five years. The control group consisted of women who had not used any hormonal contraception during this period.
**The treatment group consisted of women who received DMPA IM for five years and who were then followed up for two years after the end of use. The control group consisted of women who had not used any hormonal contraception for seven years.
SD = standard deviation
CI = confidence interval

Bone mineral density changes in adolescent females (12-18 years)
The results from an open, non-randomised, clinical study of DMPA IM (150 mg IV every twelfth week for up to 240 weeks (4.6 years), followed by measurements after the treatment) in young women (12-18 years) also showed that medroxyprogesterone acetate IM was connected with a significant reduction of BMD from the baseline. Among the trial subjects who received ≥ 4 injections/60-week period, the average reduction of BMD in the lumbar spine was 2.1% after 240 weeks (4.6 years), while the average reduction in hip and femoral neck was -6.4% and -5.4%, respectively. See table 3. In contrast to this, in a non-comparable cohort comprising non-matched, untreated trial subjects, with other baseline values for the skeletal parameters than the DMPA users, a mean increase in BMD was observed at 240 weeks at 6.4% in the lumbar spine, 1.7% in the hip and 1.9% in the femoral neck.

Table 3. Average percentage change (95% confidence interval) from the baseline of BMD in young people who received ≥ 4 injections per 60-week period, per skeletal structure

Treatment length	DMPA IM	
	N	Average % change [95% CI]
BID hip		
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]
BMD femoral neck		
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]
BMD lumbar spine		
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

Follow-up after the treatment in the same study, where young women received at least one DMPA injection and whose BMD was measured at least once after interrupting use of DMPA IM, is reported in table 4. The median number of injections in the cohort during the treatment phase was 9. When the last DMPA injection was given, the percentage BMD change from the baseline in this cohort was -2.7%, -4.1% and -3.9% in the lumbar spine, hip and femoral neck, respectively. These reduced BMD values recovered over time to the baseline value when DMPA IM had been discontinued. The time for recovery to the baseline values was 1.2 years in the lumbar spine, 4.6 years in the hip and 4.6 years in the femoral neck. It is important to note that a large number of trial subjects left the study, which is why these results are based on a small number of trial subjects, and a number of trial subjects still had a lower hip BMD after 240 weeks. A longer treatment time and smoking were connected with a slower recovery. See table 4 below.

Table 4. Average percentage change in BMD (95% confidence interval) from the baseline in young people after discontinuing DMPA

Week after discontinuing DMPA	N	Number of injections, median	Average % change (SE) from the baseline to the end of treatment	95% CI	Average % change (SE) from the baseline to the visit after DMPA	95% CI
BMD hip						
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]
BMD femoral neck						
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]
BMD lumbar spine						
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

The effect of DMPA-IM on bone mineral density (BMD) for up to 240 weeks (4.6 years) was evaluated in an open-label non-comparative clinical study of 159 adolescent females (12-18 years) who elected to begin treatment with DMPA. 114 of the 159 participants used DMPA continuously (4 injections during each 60-week period) and had BMD measured at Week 60. BMD declined significantly during the first 2 years of use with smaller change in subsequent years. After 60 weeks of DMPA use, mean percentage changes in BMD from baseline were -2.5%, -2.8% and -3.0% at the lumbar spine, hip and femoral neck, respectively. A total of 73 participants continued to use DMPA through 120 weeks, with mean BMD changes from baseline of -2.7%, -5.4% and -5.3% at the lumbar spine, hip and femoral neck, respectively. A total of 28 participants continued to use DMPA through 240 weeks, with mean BMD changes from baseline of -2.1%, -6.4% and -5.4% at the lumbar spine, hip and femoral neck, respectively.

Bone mineral density recovery post-treatment in adolescent females
In the same study, 98 adolescent women were followed who received at least 1 DMPA injection and had at least 1 follow-up BMD measurement after stopping DMPA treatment. The DMPA treatment lasted for up to 240 weeks (equivalent to 20 DMPA injections) and post-treatment follow-up extending for up to 240 weeks after the final DMPA injection. The median number of injections in this

cohort during the treatment phase was 9. At the time of the final DMPA injection, BMD changes from baseline were -2.7%, -4.1% and -3.9% at the lumbar spine, hip and femoral neck, respectively. Over time, these decreased BMD values recovered to baseline after DMPA-IM were 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 participants withdrew from the study, therefore these results are based on a small number of participants and some participants still had a deficit in total hip BMD after 240 weeks. Longer duration of treatment and smoking were associated with slower recovery.

Relationship of fracture incidence to use of DMPA injections 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' the 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 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 menopause.

5.2 Pharmacokinetic properties

The very low solubility of MPA results in an extreme prolonged-release effect. After a single injection of 150 mg intramuscularly, MPA has been able to be detected for up to 9 months. The half-life is 5-6 weeks.

5.3 Preclinical safety data

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350
Polysorbate 80
Sodium chloride
Methyl parahydroxybenzoate (E 218)
Propyl parahydroxybenzoate (E 216)
Hydrochloric acid / Sodium hydroxide (for adjustment of pH)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

The injection vial should be stored upright.
Do not refrigerate. Do not freeze.

6.5 Nature and contents of container

Suspension for injection, suspension: 1 mL, 10×3.3 mL, 10×6.7 mL in a glass vial
Suspension for injection, suspension in prefilled syringe: 1 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer AB
191 90 Sollentuna, Sweden

8 MARKETING AUTHORISATION NUMBER(S)

Suspension for injection, suspension: 9201
Suspension for injection, suspension in pre-filled syringe: 9836

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Solution for injection, suspension
Date of first authorisation: 01 October 1976
Date of latest renewal: 01 July 2006

Solution for injection, suspension in prefilled syringe
Date of first authorisation: 22 July 1982
Date of latest renewal: 01 July 2006

10 DATE OF REVISION OF THE TEXT

18 May 2021