PRODUCT MONOGRAPH

PR DEPO-PROVERA*

medroxyprogesterone acetate injectable suspension, USP

Sterile Aqueous Suspension 50 mg/mL and 150 mg/mL

PR DEPO-PROVERA*-SC

medroxyprogesterone acetate injectable suspension, house std.

Sterile Aqueous Suspension 104 mg/0.65 mL

Progestogen

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PRDEPO-PROVERA*-SC

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular (IM)	Sterile aqueous suspensions 50 mg/mL and 150 mg/mL	None are clinically relevant *For a complete listing see Dosage Forms, Composition and Packaging section.*
Subcutaneous (SC)	Sterile aqueous suspension 104 mg/0.65 mL	None are clinically relevant *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DEPO-PROVERA is indicated for:
- conception control (prevention of pregnancy)
- treatment of endometriosis

DEPO-PROVERA-SC is indicated for:
- conception control (prevention of pregnancy)

DEPO-PROVERA should be used as a birth control method or a treatment of endometriosis. DEPO-PROVERA-SC should only be used as a birth control method. DEPO-PROVERA or DEPO-PROVERA-SC should be used **only** if other treatments have been considered to be unsuitable or unacceptable and should be used for the shortest period of time possible. It should be taken into consideration that the return to fertility following treatment with DEPO-PROVERA / DEPO-PROVERA-SC may be delayed (see subsection on Sexual Function/Reproduction under **WARNINGS AND PRECAUTIONS**, and also section on FOR CONCEPTION CONTROL, under **WARNINGS AND PRECAUTIONS**).

Since loss of bone mineral density (BMD) may occur in females of child-bearing potential who use DEPO-PROVERA or DEPO-PROVERA-SC long-term (see **WARNINGS AND PRECAUTIONS**), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered. The risks and benefits of treatment should be carefully reevaluated on a regular basis in all users of this drug.

Although there are no studies addressing whether calcium and vitamin D may lessen bone mineral density (BMD) loss in women using DEPO-PROVERA or DEPO-PROVERA-SC, all patients should have adequate calcium and vitamin D intake. Cessation of smoking and regular weight bearing exercise should be discussed with all patients.

Use in Adolescents (12-18 years)
In adolescents, use of DEPO-PROVERA or DEPO-PROVERA-SC is only indicated when other contraceptive methods are considered unsuitable or unacceptable, due to unknown long-term effects of bone loss associated with DEPO-PROVERA or DEPO-PROVERA-SC during the critical period of bone accretion (see **WARNINGS AND PRECAUTIONS**).

DEPO-PROVERA-SC has not been studied in women under the age of 18 years.

CONTRAINDICATIONS

NOT FOR INTRAVENOUS USE

DEPO-PROVERA or DEPO-PROVERA-SC (medroxyprogesterone acetate) is contraindicated in women with:

- Known or suspected pregnancy or as a diagnostic test for pregnancy
- Undiagnosed vaginal and/or urinary tract bleeding
- Known or suspected carcinoma of the breast
- Undiagnosed breast pathology
- Known or suspected progestin-dependent neoplasia
- History of or actual thrombophlebitis or thromboembolic disorders
- History of or actual cerebrovascular disorders including cerebral apoplexy
- History of or actual myocardial infarction or coronary artery disease
- Presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  - Severe hypertension (persistent values of ≥160/100 mm Hg)
  - Hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden and Prothrombin G20210 A mutation, activated protein C(APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - Severe dyslipoproteinemia
  - Heavy smoking (>15 cigarettes per day) and over age 35
  - Diabetes mellitus with vascular involvement
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields

- Current or history of migraine with focal aura
- Active liver disease or history of or actual benign or malignant liver tumours
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

DEPO-PROVERA or DEPO-PROVERA-SC should not be used before menarche.

Serious Warnings and Precautions

The use of DEPO-PROVERA or DEPO-PROVERA-SC has been associated with loss of bone mineral density (BMD) which may not be completely reversible. Loss of bone mineral density is greater with increasing duration of use.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if the use of DEPO-PROVERA or DEPO-PROVERA-SC during adolescence or early adulthood will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. A study to assess effects of MPA-IM in adolescent females showed that its use was associated with significant decline in BMD from baseline, and that mean BMD loss at total hip and femoral neck did not fully recover by 60 months (240 weeks) post-treatment. Similarly, in adults, there was only partial recovery of mean BMD at total hip, femoral neck and lumbar spine towards baseline by 24 months post-treatment.

DEPO-PROVERA or DEPO-PROVERA-SC should be used as indicated **only** if other treatments have been considered to be unsuitable or unacceptable and should be used for the shortest period of time possible.

The risks and benefits of treatment should be carefully reevaluated on a regular basis in all users of this drug.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Women should be counseled not to smoke.

This product does not protect against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs it is advisable to use latex or polyurethane condoms.

WARNINGS AND PRECAUTIONS

1 – GENERAL

General

Discontinue Medication at the Earliest Manifestation of:

A. **Thromboembolic and cardiovascular disorders** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis and retinal thrombosis;
B. **Conditions that predispose to venous stasis and vascular thrombosis**, such as immobilization after accidents or confinement to bed during long-term illness. Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of hormonal contraceptives when surgery is contemplated, see **Peri-operative Considerations below**:
C. **Visual defects-partial or complete**
D. **Papilledema or ophthalmic (retinal) vascular lesions**
E. **Severe headache of unknown etiology or worsening of pre-existing migraine headache.**

Carcinogenesis and Mutagenesis

Long-term, case-controlled surveillance of users of DEPO-PROVERA found slight or no increased overall risk of breast cancer and 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

The World Health Organization Study, a component of a pooled analysis, showed an increased RR of 2.19 (95% CI 1.23 to 3.89) of breast cancer associated with the use of DEPO-PROVERA in women whose first exposure to drug was within the previous 4 years and who were under 35 years of age. However, the overall RR for women who have ever used DEPO-PROVERA was only 1.2 (95% CI 0.96 to 1.52).

[NOTE: A RR of 1.0 indicates neither an increased nor a decreased risk of cancer associated with the use of the drug, relative to no use of the drug. In the case of the subpopulation with a RR of 2.19, the 95% CI is fairly wide and does not include the value of 1.0, thus inferring an increased risk of breast cancer in the defined subgroup relative to nonusers. The value of 2.19 means that women whose first exposure to drug was within the previous 4 years and who are under 35 years of age have a 2.19-fold (95% CI 1.23 to 3.89-fold) increased risk of breast cancer relative to nonusers. The National Cancer Institute reports an average annual incidence rate for breast cancer for US women, all races, age 30 to 34 years of 26.7 per 100,000. A RR of 2.19, thus, increases the possible risk from 26.7 to 58.5 cases per 100,000 women. The attributable risk, thus, is 31.8 per 100,000 women per year.]

Women who currently have or have had breast cancer should not use hormone contraceptives, including DEPO-PROVERA, because breast cancer may be hormonally sensitive. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Women receiving DEPO-PROVERA should be counselled regarding the importance of breast self-examination. Clinical breast examination should be performed at regular intervals.

Cervical Cancer
A statistically insignificant increase in RR estimates of invasive squamous-cell cervical cancer has been associated with the use of DEPO-PROVERA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93 to 1.70). The overall, nonsignificant relative rate of invasive squamous-cell cervical cancer in women who ever used DEPO-PROVERA was estimated to be 1.11 (95% CI 0.96 to 1.29). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Cardiovascular

Thromboembolic Disorders
Although DEPO-PROVERA has not been causally associated with the induction of thrombotic or thromboembolic disorders, there have been reports of cerebrovascular and thromboembolic adverse events in obese DEPO-PROVERA women. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of DEPO-PROVERA use in this population. Before prescribing DEPO-PROVERA or DEPO-PROVERA-SC, the physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Predisposing Factors for Coronary Artery Disease
Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Convincing data are available to support an upper age limit of 35 years for hormonal contraceptive use by women who smoke.

Other women who are independently at high risk for cardiovascular disease include those who suffer from or have a family history of diabetes, hypertension or an abnormal lipid profile. Whether hormonal contraceptives accentuate this risk is unclear.

There have been post-market reports of cardiovascular events, including heart attack and stroke (e.g. medullary infarction in a heavy smoker) in women using DEPO-PROVERA (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**). Generally, it is not clear if the risk of cardiovascular events is different for users of DEPO-PROVERA than for non-users.

Hypertension
There have been reports of cerebro/cardiovascular adverse events in DEPO-PROVERA users who are suffering from hypertension. Patients with essential hypertension whose blood pressure is well

controlled may be given hormonal contraceptives but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary (see also **CONTRAINDICATIONS**).

Endocrine and Metabolism

Loss of Bone Mineral Density

Use of DEPO-PROVERA or DEPO-PROVERA-SC reduces serum estrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if the use of DEPO-PROVERA or DEPO-PROVERA-SC by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life. In both adult and adolescent females the decrease in BMD during treatment appears to be substantially reversible after MPA injection is discontinued and ovarian estrogen production increases.

A retrospective cohort study to assess the effect of MPA injection on the incidence of bone fractures was conducted in 312,395 female contraceptive users in the UK. The incidence rates of fracture were compared between MPA users and contraceptive users who had no recorded use of MPA. The Incident Rate Ratio (IRR) for any fracture during the follow-up period (mean = 5.5 years) was 1.41 (95% CI 1.35, 1.47). Among the sub-cohort with data before and after first reported contraceptive treatment (N=166,367), comparisons were made for the follow-up period and also for the 6-month period prior to first reported contraceptive treatment. Comparing MPA users to non-users, the IRR for any fracture 'before treatment' (IRR 1.28, 95 % CI 1.07, 1.53) was comparable to the IRR 'after treatment' (IRR 1.37, 95% CI 1.29, 1.45). The overall results support the conclusion that the higher observed incidence of fractures among MPA users in this study was principally a result of factors other than exposure to MPA**.**

Long term use:
BMD should be monitored in women using DEPO-PROVERA or DEPO-PROVERA-SC for longer than 2 years, or earlier as clinically appropriate. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. If a clinically significant decrease in BMD is detected, treatment with DEPO-PROVERA or DEPO-PROVERA-SC should be reconsidered.

Use of DEPO-PROVERA or DEPO-PROVERA-SC should be considered a risk factor for osteoporosis. The use of DEPO-PROVERA or DEPO-PROVERA-SC should be considered in light of a patient's possible other risk factors for osteoporosis: Chronic alcohol 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
- Metabolic bone disease
- Strong family history of osteoporosis

BMD Changes in Adult Women

In a controlled, open-label, non-randomized clinical study (DEPO-PROVERA n=248, placebo n=360), adult women using DEPO-PROVERA (150 mg IM) for up to 5 years for contraception 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 2 years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Table 1 shows the extent of recovery of BMD for women who received one or more DEPO-PROVERA injections during Years 1 through 5.

Table 1. Mean Percent Change from Baseline in BMD in Adults by Skeletal Site and Cohort (ITT Population*)

Time in Study	Lumbar Spine		Total Hip		Femoral Neck	
	Depo-Provera**	Control***	Depo-Provera**	Control***	Depo-Provera**	Control***
1 year	n=135 -2.86%	n=253 0.22%	n=88 -1.56%	n=125 0.95%	n=137 -2.85%	n=254 0.28%
2 years	n=94 -4.11%	n=197 0.29%	n=57 -3.06%	n=94 0.69%	n=95 -3.99%	n=195 -0.22%
3 years	n=71 -4.89%	n=159 0.31%	n=42 -3.89%	n=77 -0.06%	n=72 -4.80%	n=159 -0.23%
4 years	n=59 -4.93%	n=137 0.35%	n=31 -4.52%	n=70 -0.02%	n=58 -5.90%	n=138 -0.53%
5 years	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
Post-therapy † Year 1	n=45 -2.42%	n=87 0.28%	n=31 -0.70%	n=54 0.65%	n=45 -3.04%	n=86 -0.27%
Post-therapy † Year 2	n=41 -1.19%	n=66 0.47%	n=25 -0.20%	n=43 0.84%	n=42 -3.11%	n=69 -0.36%

* *Intent-to-treat population consisted of patients who enrolled in the study and had BMD measured at screening/baseline and at least one post-baseline time point.*

** *MPA group consisted of women who received one or more MPA injections during Years 1 through 5.*

*** *The control group consisted of women who did not use Depo-Provera prior to the indicated time point.*

† *Women who took one or more doses of Depo-Provera, and then stopped treatment, entered the Post-therapy phase of the study; BMD results from such subjects would no longer be reported in the on-therapy section of the Table. For Control women, results from Years 6 and 7 are shown in the Post-therapy section.*

After stopping use of DEPO-PROVERA (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2-years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a less complete BMD recovery observed during the 2–year, post-therapy period.

BMD Changes in Adolescent Females (12-18 years)

An open-label, non-randomized clinical study of DEPO-PROVERA-injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception (DEPO-PROVERA n=177, Control n=237), also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline (Table 2). However, adolescent girls in an unmatched control group showed an increase in BMD during this period of growth following menarche. The two cohorts of this open-label study were not matched at baseline for age, race, BMD and other factors that affect the rate of acquisition of BMD.

Table 2. Mean Percent Changes from Baseline Bone Mineral Density (BMD) and Bone Mineral Content (BMC) for Adolescents on DEPO-PROVERA (Regular Users) and Unmatched, Untreated Controls

	DMPA**		**Unmatched Control*****	
	N	% Change (SD)	N	% Change (SD)
Lumbar Spine BMD				
On Treatment 60 wk	114	-2.5 (2.6)	167	3.4 (3.3)
On Treatment 120 wk	73	-2.7 (3.6)	109	5.3 (5.6)
On Treatment 240 wk	27	-2.1 (5.2)	84	6.4 (6.8)
Post-treatment 60 wk*	70	0.5 (5.6)	67	7.6 (6.7)
Post-treatment 120 wk*	52	2.4 (5.2)	63	9.1 (7.8)
Post-treatment 180 wk	39	3.5 (5.0)	N/A§	N/A§
Post-treatment 240 wk	25	4.7 (5.1)	N/A§	N/A§
Total Hip BMD				
On Treatment 60 wk	113	-2.8 (3.1)	166	1.2 (2.8)
On Treatment 120 wk	73	-5.4 (3.3)	108	2.2 (4.5)
On Treatment 240 wk	28	-6.4 (5.6)	84	1.7 (5.7)
Post-treatment 60 wk*	71	-2.5 (4.8)	67	2.0 (6.7)
Post-treatment 120 wk*	52	-1.6 (5.0)	62	2.2 (7.0)
Post-treatment 180 wk	39	-0.6 (5.2)	N/A§	N/A§
Post-treatment 240 wk	25	0.3 (5.0)	N/A§	N/A§
Femoral Neck BMD				
On Treatment 60 wk	113	-3.0 (4.2)	166	1.8 (3.6)
On Treatment 120 wk	73	-5.3 (4.0)	108	2.8 (5.4)
On Treatment 240 wk	28	-5.4 (6.2)	84	1.9 (6.5)
Post-treatment 60 wk*	71	-3.3 (5.9)	67	2.1 (7.3)
Post-treatment 120 wk*	52	-1.7 (5.7)	62	2.5 (7.8)
Post-treatment 180 wk	39	-0.7 (5.9)	N/A§	N/A§
Post-treatment 240 wk	25	-0.8 (6.2)	N/A§	N/A§
Whole Body BMC				
On Treatment 60 wk	112	0.9 (3.5)	165	4.4 (4.3)
On Treatment 120 wk	73	1.3 (4.8)	109	7.5 (7.1)
On Treatment 240 wk	28	3.6 (8.1)	85	9.3 (8.6)
Post-treatment 60 wk*	67	3.7 (5.3)	66	11.5 (9.9)
Post-treatment 120 wk*	50	5.3 (7.0)	62	12.7 (10.1)
Post-treatment 180 wk	39	6.1 (6.9)	N/A§	N/A§
Post-treatment 240 wk	25	8.7 (6.1)	N/A§	N/A§
Lumbar Spine BMC				
On Treatment 60 wk	114	-2.68 (3.91)	167	5.98 (5.43)

On Treatment 120 wk	73	-2.11 (5.49)	109	9.62 (9.36)
On Treatment 240 wk	27	-0.27 (8.32)	84	12.44 (12.32)
Total Hip BMC				
On Treatment 60 wk	113	-1.52 (4.23)	166	2.67 (3.79)
On Treatment 120 wk	73	-4.20 (4.78)	108	4.03 (5.78)
On Treatment 240 wk	28	-4.94 (8.15)	84	3.05 (6.86)
Femoral Neck BMC				
On Treatment 60 wk	113	-2.83 (5.41)	166	2.92 (4.95)
On Treatment 120 wk	73	-4.45 (5.70)	108	4.11 (7.11)
On Treatment 240 wk	28	-5.26 (7.21)	84	3.72 (9.39)

* For unmatched control group, PT 60 wk represents 300 wk follow-up; PT 120 wk represents 360 wk follow-up. ** On-treatment results for DMPA group include only subjects who had uninterrupted use of DMPA through each follow-up time point; PT results include all subjects who received ≥1 DMPA injection and had a post-treatment DXA scan. *** Control subjects were not matched for age, race, or other factors affecting bone metabolism; they differed significantly from DMPA subjects and valid comparison of BMD or BMC changes between the groups is not possible. § Maximum observation time was 360 weeks (240 wks + 120 wks) in control group; in DMPA group, PT observation through 180 wks and 240 wks was possible if DMPA treatment time was no more than 180 wks and 120 wks, respectively, for a combined total of 360 wks.

In addition to BMD results, Table 2 also shows the % changes (vs. baseline) in Bone Mineral Content (BMC). Whole body BMC is a measure of the overall mineral content of the skeleton. Unlike the adult skeleton, that of the adolescent is growing in size. Therefore, while examination of BMD changes is generally sufficient for understanding the adult subject, both BMD and BMC should be assessed together in the adolescent.

The results in Table 2 indicate that in the Depo-Provera group, mean lumbar spine BMC decreased up to Week 120, but thereafter showed increases toward baseline levels; hip and femoral neck mean BMC was decreased at all time points, while total body BMC was increased compared to baseline at all time points. Mean BMC in the non-Depo-Provera group was increased from baseline at all sites and time points, including total body BMC.

Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was - 2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. Post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued and that hip BMD recovered to baseline levels approximately 5 years after treatment was discontinued. Femoral neck BMD recovered to post-treatment baseline levels in approximately 5 years. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

In post-marketing experience, there have been cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA. Patient age ranged from 16 years to 48 years (see **Post-Market Adverse Drug Reactions**).

Adrenocortical Function

Clinical suppression of adrenocortical functions has not been observed at low dose levels used for contraception (ovulation suppression).

Carbohydrate Metabolism
A decrease in glucose tolerance has been observed in some women receiving DEPO-PROVERA. The mechanisms of this decrease are obscure. For this reason, diabetic women should be carefully observed while receiving DEPO-PROVERA.

Fluid Retention
Since progestogens may cause some degree of fluid retention, conditions that might be influenced by this factor, such as migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight Changes
Weight gain may be associated with the use of DEPO-PROVERA (see **ADVERSE REACTIONS**). The majority of studies report a mean weight gain of 5.4 lbs (2.5 kg) at the end of 1 year, but only 2% of women discontinued treatment due to excessive weight gain (see **Clinical Trial Adverse Drug Reactions, Weight Gain Experience**). Many studies indicate that weight gain occurs mainly in the first year of use, however, others do report a slow and continuing increase which may reach a mean of 8 lbs (3.6 kg) by the end of 2 years. Some 20 to 40 percent of DEPO-PROVERA users actually lose weight during treatment.

A mean increase from pretreatment to 12 months of 1.6 kg was observed in subjects treated with DEPO-PROVERA-SC; this increase was less than the mean weight increase of 2.5 kg observed after 1 year of treatment in previous studies of MPA-IM.

General disorders and administration site conditions
Injection Site Reactions
In 3 clinical studies of DEPO-PROVERA-SC involving 2,043 women, 5.4% of women experienced injection site reaction events that were considered drug related. None was classified as serious.

Genitourinary

Irregular Menstrual Patterns
Disruption of menstrual patterns is common following the administration of DEPO-PROVERA. This includes irregular or unpredictable bleeding or spotting, or rarely heavy or continuous bleeding. If undiagnosed vaginal bleeding occurs, or if abnormal bleeding persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology, and appropriate treatment instituted if necessary.

As women continue to use DEPO-PROVERA, fewer experience irregular bleeding patterns and more experience amenorrhea. By month 12, amenorrhea was reported by 55% of women, and by month 24, amenorrhea was reported by 68% of women using DEPO-PROVERA.

Because of the prolonged effect following intramuscular injection of DEPO-PROVERA, re-establishment of menstruation may be delayed and difficult to predict. For this reason, DEPO-PROVERA is not recommended for treatment of secondary amenorrhea or functional uterine bleeding. For these conditions, oral progestogen therapy is recommended.

Most women using DEPO-PROVERA-SC experienced alteration of menstrual bleeding patterns.

Patients should be appropriately counseled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. As women continued using DEPO-PROVERA-SC, fewer experienced irregular bleeding and more experienced amenorrhea. After receiving the fourth dose, 39% of women experienced amenorrhea during month 6. During month twelve, 56.5% of women experienced amenorrhea. The changes in menstrual patterns from the three contraception trials are presented in Figures 1 and 2. Figure 1 shows the increase in the percentage of women experiencing amenorrhea over the 12 month study. Figure 2 presents the percentage of women experiencing spotting only, bleeding only, and bleeding and spotting over the same time period. In addition to amenorrhea, altered bleeding patterns included intermenstrual bleeding, menorrhagia and metrorrhagia. If abnormal bleeding associated with DEPO-PROVERA-SC persists or is severe, appropriate investigation and treatment should be instituted.

Figure 1. Percent of DEPO-PROVERA-SC -Treated Women with Amenorrhea per 30-Day Month Contraception Studies (ITT Population, N=2053)

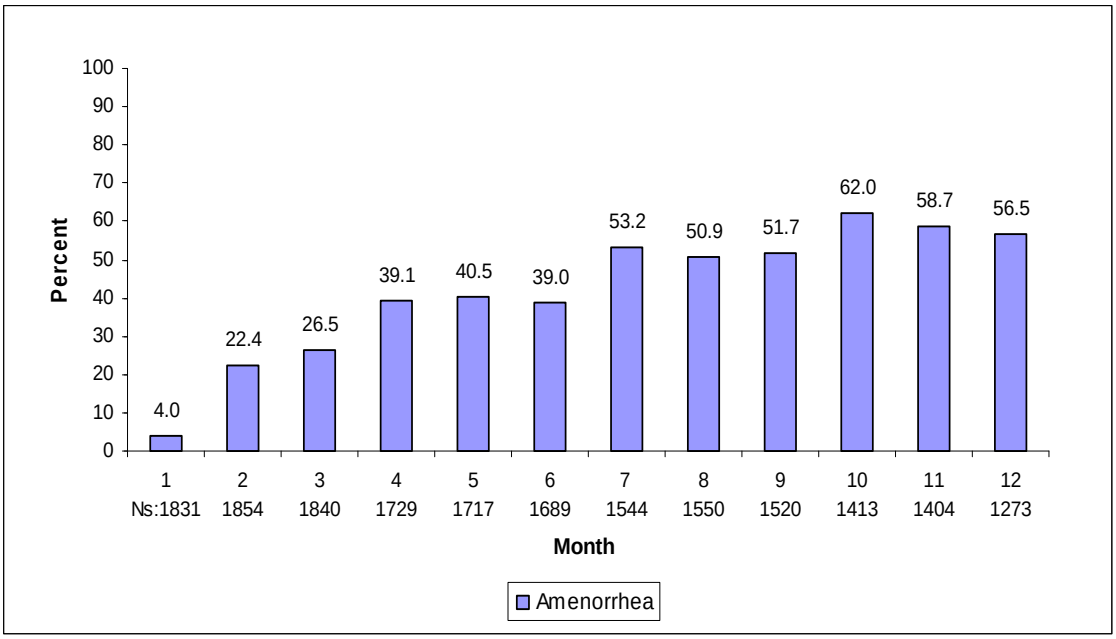
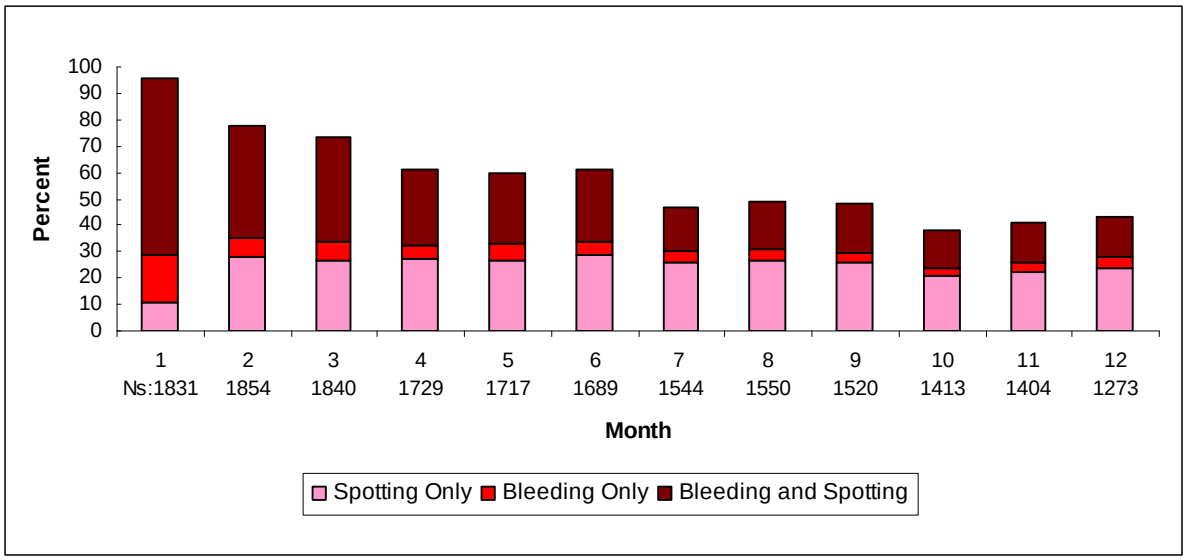


Figure 2. Percent of DEPO-PROVERA-SC -Treated Women with Bleeding and/or Spotting per 30-Day Month Contraception Studies (ITT Population, N=2053)



Hematologic

There have been post-market reports of arterial and venous thromboembolism (VTE) in women using DEPO-PROVERA (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**). Generally, it is not clear if the risk of arterial and venous thromboembolism is different for users of DEPO-PROVERA than for non-users.

Generalized risk factors for venous thromboembolism include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index >30kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking. The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma.

Hepatic/Biliary/Pancreatic

Liver function tests should be performed periodically in women who are suspected of, or who are at risk of, having hepatic disease. The physician should be alert to the earliest manifestations of impaired liver function. Should this occur or be suspected, the treatment should not be continued. The woman's status should be re-evaluated at appropriate intervals. If jaundice develops, consideration should be given to discontinue the drug.

Patients who have had jaundice, including a history of cholestatic jaundice during pregnancy or during use of oral contraceptives should be given hormonal contraceptives only with great care and under close observation.

Immune

Anaphylactic Reactions
Anaphylactic and anaphylactoid reactions have occasionally been reported in women treated with DEPO-PROVERA. If an anaphylactic reaction occurs, appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

Neurologic

CNS Disorders and Convulsions
There have been few reported cases of convulsions in patients who were treated with DEPO-PROVERA. Association with DEPO-PROVERA use or pre-existing conditions is not clear. Women with known seizure disorders, including epilepsy, require careful observation.

Migraine and Headache
The onset or exacerbation of migraine or the development of headaches with a new pattern that is recurrent, persistent or severe requires discontinuation of hormonal contraceptives and evaluation of the cause.

Women with migraine headache who take hormonal contraceptives may be at increased risk of stroke (see **CONTRAINDICATIONS**).

Ophthalmologic

Ocular Disorders
Discontinue medication pending examination, if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Peri-operative Considerations

If feasible, hormonal contraceptives should be discontinued and an alternative method substituted at least four weeks prior to elective surgery of a type associated with an increase in risk of thromboembolism and during prolonged immobilization. Hormonal contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery or following prolonged immobilization.

Psychiatric

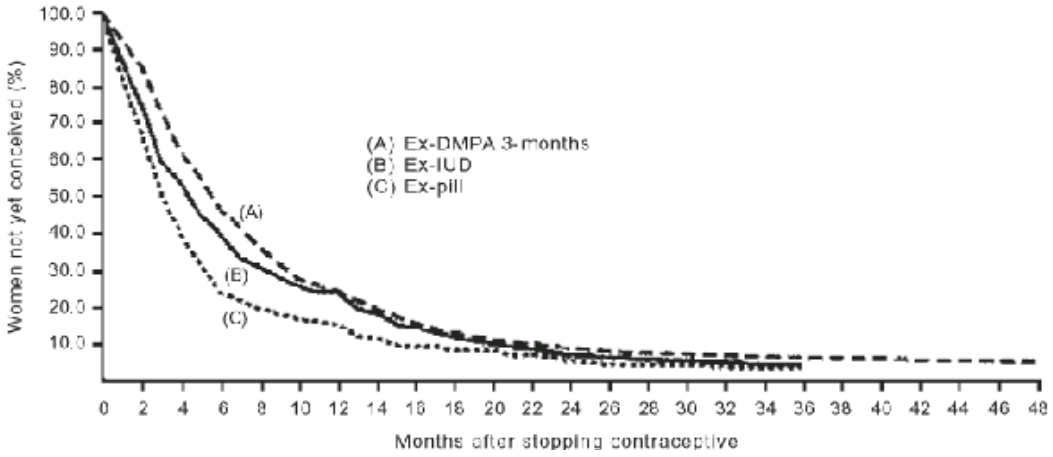
Women who have a history of mental depression should be carefully observed and this drug discontinued if serious depression re-occurs. Some women may complain of premenstrual like depression while on DEPO-PROVERA therapy.

Sexual Function/Reproduction

Return of Fertility

There is no evidence that DEPO-PROVERA causes infertility. A large study of return of fertility shows that women conceived 9 months on average after the last injection, or 5.5 months after discontinuing (discontinuance is assumed to be 15 weeks after the last injection). In addition, the number of users who had conceived within 2 years of discontinuing their method of contraception (92% of DEPO-PROVERA users had conceived within 2 years after discontinuing compared with 93% for users of the IUD and 95% for users of oral contraceptives) were comparable. Discuss this information with women who intend to conceive in the next 1 to 2 years.

Cumulative conception rates for women discontinuing use of an IUD, oral contraceptives, or DEPO-PROVERA in order to become pregnant



In some cases, women have not become pregnant after stopping injections of DEPO-PROVERA. It is not known whether DEPO-PROVERA or other factors resulted in a change in the ability to conceive. Many reasons exist for such changes, including increased age and the onset of menopause. The infertility rate in the normal population is 7%.

The time to return to fertility for DEPO-PROVERA-SC has not been measured in a large population. Among 21 women using DEPO-PROVERA-SC for contraception who stopped treatment to become pregnant, 1 became pregnant within 1 year of her last injection. A second woman became pregnant 443 days after her last injection. Seven women were lost to follow-up.

Ectopic pregnancy

Physicians should investigate the possibility of an ectopic pregnancy among women using DEPO-PROVERA or DEPO-PROVERA-SC who complain of severe abdominal pain.

Special Populations

Pregnant Women:

To increase assurance that the woman is not pregnant at the time of the first administration, it is recommended that the first injection be given only within the first 5 days of the onset of a normal

menstrual period or, only within the first 5 days post-partum if not breast-feeding (see **DOSAGE and ADMINISTRATION**).

Infants from unexpected pregnancies that occurred 1 to 2 months after injection of DEPO-PROVERA or DEPO-PROVERA-SC may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in incidence of polysyndactyly and chromosomal anomalies was observed among infants of users of DEPO-PROVERA, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-PROVERA and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Children exposed to medroxyprogesterone acetate *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual, or social development.

Several reports suggest an association between intra-uterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1,000 male births in the general population) may be approximately doubled with exposure to these drugs. Although there are insufficient data to quantify the risk to exposed female fetuses, some of these drugs induce mild virilization of the external genitalia of the female fetus. Because of these changes, it is prudent to avoid the use of progestogens during the first trimester of pregnancy.

Although a causal relationship between DEPO-PROVERA and the induction of thrombotic or thromboembolic disorders has not been determined, in post-marketing experience, cases of cerebro/cardiovascular and thromboembolic adverse events occurring 48 hours to 2 months after delivery have been reported. Women should be encouraged to consider a form of contraception that does not increase the risk of the above-noted events in the three months post-partum, if possible.

Nursing Women:
Detectable amounts of progestogen have been identified in the milk of mothers receiving DEPO-PROVERA. Two studies have indicated that the maximum amount of medroxyprogesterone acetate (MPA) which might be ingested by a breast-feeding infant whose mother is receiving DEPO-PROVERA for contraception would be 1.0 to 1.5 µg/day (or 0.0015 mg/day, 0.045 mg/month, 0.27 mg over 6 months which is about 0.05 mg/kg over 6 months for a 5.5 kg baby). If absorption properties between adult and infant are comparable, this amount would be too low to suppress pituitary function in the infant. No adverse effects related to lactation itself or infant growth were reported in studies where DEPO-PROVERA was started 1-4 days, 7 days or within 6 weeks postpartum.

In nursing mothers treated with DEPO-PROVERA, milk composition, quality and amount are not adversely affected.

To date, no adverse effects have been observed in children whose mothers were using DEPO-PROVERA while lactating. A study of children exposed to MPA with median observation periods of 14 - 16 years, indicated no incidence of adverse effects on physical growth, mental growth and development of general health status. However, the long-term effects on the child are not fully understood. It is recommended that DEPO-PROVERA not be administered until 6 weeks postpartum in women who are breast feeding to avoid risk of exposure of the neonate to steroid hormones. The physician and woman should discuss the risks of pregnancy versus the risks to the child, if DEPO-PROVERA is used during lactation, to determine the most appropriate course of action for the individual woman. This discussion should take into account that there have been post-marketing reports of low birth weights and neonatal feeding disorders in children whose mothers were using DEPO-PROVERA while lactating.

Pediatrics
DEPO-PROVERA or DEPO-PROVERA-SC should not be used before menarche (see **CONTRAINDICATIONS**).

Other
In the perimenopausal population, age constitutes no absolute limiting factor, although treatment with a progestogen may mask the onset of the climacteric.

Monitoring and Laboratory Tests
Before DEPO-PROVERA or DEPO-PROVERA-SC is used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active. The first follow-up visit should be three months after the initiation of therapy. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. At each visit, examination should include those procedures that were done at the initial visit, as outlined above or as per the recommendations of the Canadian Task force on the Periodic Health Examination.

Bone mineral density (BMD) should be monitored in women using DEPO-PROVERA or DEPO-PROVERA-SC for longer than 2 years, or earlier as clinically appropriate. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. If a clinically significant decrease in BMD is detected, treatment with DEPO-PROVERA or DEPO-PROVERA-SC should be reconsidered. (See **WARNINGS AND PRECAUTIONS, Loss of Bone Mineral Density)**.

2 - FOR CONCEPTION CONTROL

Counseling
It is very important that adequate explanations of the long-term nature of DEPO-PROVERA or DEPO-PROVERA-SC as a contraceptive be given to each woman prior to her first injection. The possible side effects including BMD changes, changes in menstrual cycle and the relatively slow return of fertility should be emphasized. Every effort should be made to ensure that each woman receives such counseling as to enable her to understand fully these

explanations and the possible consequences. A detailed Patient Information leaflet that describes the actions, benefits, risks and adverse effects of this contraceptive should be made available to each woman before she makes the decision to use DEPO-PROVERA or DEPO-PROVERA-SC for conception control.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following adverse reactions have been associated with the use of DEPO-PROVERA (medroxyprogesterone acetate):

(A) Irregular Menstrual Patterns
The most common adverse reactions associated with the use of DEPO-PROVERA for contraception is the disruption of menstrual patterns. This includes irregular or unpredictable bleeding or spotting, or rarely heavy or continuous bleeding.

(B) Non-Menstrual Adverse Reactions
Other than menstrual changes, weight gain, headache and abdominal discomfort are the most common side effects.

In a few instances there have been undesirable sequelae at the site of injection, such as a residual lump, change in colour of the skin or a sterile abscess.

Anaphylactic and anaphylactoid reactions have been reported on rare occasions.

The following adverse reactions have been associated with the use of DEPO-PROVERA-SC:

Two thousand and fifty-three (2053) patients received subcutaneous medroxyprogesterone acetate in the 3 Phase 3 clinical trials.
Adverse events of any cause were reported for 59.5% (1216/2043) of the MPA-SC group. The most frequently reported adverse events were headache (8.5%, 173/2043), intermenstrual bleeding (7.1%, 145/2043), weight increased (6.9%, 140/2043), and amenorrhea not otherwise specified (NOS) (6.4%, 130/2043). Table 5 displays adverse events that were reported in at least 1% of the subjects treated with MPA-SC. Most reported adverse events and drug-related adverse events were mild or moderate in intensity.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

DEPO-PROVERA

In clinical studies of 3,905 women receiving DEPO-PROVERA every 3 months, there were a total of 8,467 side effect reports. Headache, abdominal distress, nervousness, dizziness and decreased libido were reported in greater than 5.0 percent of study patients. Thrombophlebitis was reported by 4 women (0.10%).

(A) Total Adverse Reaction Experience:
Table 3 contains a list of reported side effects, the number of times each side effect was reported and the number and percent of patients who reported each side effect. Table 4 contains the number of side effects reported by month and the number of side effect reports per 100 patients "exposed" by month.

TABLE 3			
DEPO-PROVERA EVERY 90 DAYS SIDE EFFECTS			
Symptom	**No. of Times Reported**	**No. of Women Reporting**	**Percent of Women (3,905)**
Headache	2187	682	17.46
Abdominal Distress	990	463	11.85
Nervousness	1143	451	11.55
Dizziness	411	232	5.94
Decreased Libido	541	225	5.76
Asthenia	321	177	4.53
Limb Pain & Varicose Vein Pain	311	152	3.89
Nausea	209	138	3.53
Vaginal Discharge	178	120	3.07
Breast Swelling & Tenderness	188	114	2.92
Bloating	170	94	2.41
Edema Peripheral	170	87	2.22
Backache	131	87	2.22
Dysmenorrhea	95	69	1.77
Depression	100	62	1.59
Acne	72	48	1.23
Pruritus Vulvae	67	48	1.23
No Hair Growth, Alopecia	108	46	1.18
Rash	78	41	1.05
Hot Flash	51	40	1.02
Insomnia	54	38	0.97
Genitourinary Infection	45	34	0.87
Eye Discomfort	45	33	0.85
Anorexia	37	29	0.74
Increased Appetite	37	28	0.72
Chest Pain	33	28	0.72
Dysuria	39	28	0.72
Diarrhea	28	25	0.64
Heartburn	26	23	0.59
Galactorrhea	40	22	0.56
Pruritus	28	22	0.56
D&C for Bleeding	21	21	0.54
Pain	25	19	0.49
Somnolence Drowsiness	23	19	0.49
Dyspareunia	21	17	0.43
Dyspnea	30	17	0.43
Abdominal Swelling	25	17	0.43
Allergic Reactions	21	15	0.38
Chloasma	26	13	0.33

TABLE 3			
DEPO-PROVERA EVERY 90 DAYS SIDE EFFECTS			
Symptom	**No. of Times Reported**	**No. of Women Reporting**	**Percent of Women (3,905)**
Vomiting	16	12	0.31
Constipation	19	11	0.28
Tachycardia	11	10	0.26
Liver disorders NOS, altered liver function	14	10	0.26
Hirsutism	13	10	0.26
Frequency Urination	11	10	0.26
Paraesthesia, Sensory Disturbances	13	9	0.23

According to Table 4, 1,135 (13.40%) of the total 8,467 side effect reports were reported during the first injection period (90 days); during the first two injection periods (first 180 days) 2,070 (24.45%) were reported; 2,826 (33.38%) were reported during the first three injection periods (first 270 days); and 3,536 (41.75%) were reported during the first four injection periods (first 360 days). The number of patients not reporting any side effects was 2,117 (54.2%).

TABLE 4			
DEPO-PROVERA EVERY 90 DAYS - SIDE EFFECTS (BY MONTH)			
Month	**# Pts Entering/Month**	**# Reports**	**# Reports/100 Patients**
1	3905	355	9.09
2	3670	373	10.16
3	3571	407	11.40
4	3294	290	8.80
5	3084	283	9.18
6	3004	362	12.05
7	2792	249	8.91
8	2634	218	8.28
9	2579	289	11.22
10	2419	224	9.26
11	2299	220	9.57
12	2253	266	11.81
15	1872	212	11.32
18	1659	225	13.56
21	1485	198	13.33
24	1344	194	14.43
27	1180	155	13.14
30	1037	124	11.96
33	927	127	13.70
36	827	128	15.48
39	722	112	15.51
42	664	99	14.91
45	573	84	14.66
48	474	45	9.49
51	412	52	12.62
54	350	46	13.14
57	305	44	14.43
60	263	23	8.75
63	227	19	8.37
66	201	20	9.95
69	184	17	9.24
72	157	17	10.83

TABLE 4			
DEPO-PROVERA EVERY 90 DAYS - SIDE EFFECTS (BY MONTH)			
Month	**# Pts Entering/Month**	**# Reports**	**# Reports/100 Patients**
75	118	12	9.32
78	91	16	17.58
81	49	3	6.12
84	1	0	0.00

Bleeding Experience:

In U.S. studies of 3,905 women receiving DEPO-PROVERA every 3 months, unpredictable bleeding or spotting were commonly reported during the first few menstrual cycles with frequency, duration and amount of bleeding diminishing gradually. By month 12, amenorrhea was reported by 55% of the women, and by month 24, amenorrhea was reported by 68% of the women using DEPO-PROVERA. Bleeding or spotting persisted for more than 10 days of the month in about 12% of the users. Abnormally heavy or prolonged bleeding occurred in about 1 to 2% of users.

The percent of patients with zero days of bleeding and/or spotting per 30-day month increases with time from start of study, as follows:

Month	**Percent Having Zero Bleeding and/or Spotting**
3	29.3
12	54.6
24	67.7
36	73.8
48	75.5
60	79.3
72	78.9

Bleeding and/or spotting occurred in the following percentage of the 90 days of the indicated injection period.

Injection Period	Months	Percent of Days with Bleeding and/or Spotting
First	1 – 3	25.7
Fourth	10 – 12	11.8
Eighth	22 – 24	6.8
Twelfth	34 – 36	4.8
Sixteenth	46 – 48	4.3
Twentieth	58 – 60	4.1
Twenty-fourth	70 – 72	4.3

On hundred and ninety four (194) patients reported no bleeding or spotting from first injection to the end of their participation in the study. The median number of days of no spotting or bleeding

for these 194 women was 120 days. The minimum number of days of no spotting or bleeding was 30 and the maximum was 1,674 days.

Thirteen (13) patients reported bleeding and/or spotting every day from first injection to the end of their participation in the study.

Weight Gain Experience:
The U.S. studies of 3,905 women receiving DEPO-PROVERA every 3 months report a mean weight gain of 5.4 lbs (2.5 kg) at the end of 1 year, but only 2% of women discontinued treatment due to excessive weight gain. Many studies indicate that weight gain occurs mainly in the first year of use, however, others report a slow and continuing increase which may reach a mean of 8 lbs (3.6 kg) by the end of 2 years. However, some 20 to 40 percent of DEPO-PROVERA users actually lose weight during treatment.

A much higher proportion of patients had an increase as had a decrease of more than 15 pounds. The mean body weight changes from baseline (in pounds) were as follows:

Month	Weight Increase(pounds)	n
12	5.4	1,644
24	8.1	960
36	11.3	567
48	13.8	282
60	14.1	150
72	16.5	109

Laboratory Assay Results
Laboratory assays were performed on a sample of women, rather than on all women. There were no clinically significant changes in any of the haematology, urine or serum chemistry variables that were monitored.

The number of women having had an initial Pap smear taken is 2,052. Ten (10) patients dropped from the study due to a Grade IV Pap smear, while 4 patients dropped out due to a Grade III Pap smear.

(B) Non-Menstrual Adverse Reactions:
The occurrence rates for non-menstrual adverse reactions reported in U.S. studies of 3,905 women receiving DEPO-PROVERA every 3 months are listed below. 2,253 women were in the study for 12 months or more; 827 women were in the study for 36 months or more. The total number of patient-months of experience was 82,384. A total of 2,117 of the 3,905 women (54%) reported no side effects.

SYSTEM ORGAN CLASS	EVENT
General disorders and administration site conditions	Asthenia (5%) Peripheral edema (2%) The following adverse events occurred in less than 1% of patients: Axillary swelling, pain, chills, excessive thirst, fever, pain at injection site

SYSTEM ORGAN CLASS	EVENT
Blood and lymphatic system disorders	The following adverse events occurred in less than 1% of patients: Anemia, blood dyscrasia
Cardiac disorders	Chest pain, tachycardia (0.2 - 1.0%)
Eye disorders	Eye discomfort (0.2 - 1.0%)
Gastrointestinal disorders	Abdominal distress (12%) Nausea (4%) Bloating (2%) Anorexia, increased appetite, diarrhea, heartburn, abdominal swelling, vomiting, constipation (0.2 - 1.0%) The following adverse events occurred in less than 1% of patients: Gastro-intestinal disturbances, rectal bleeding
Hepatobiliary disorders	Liver disorders NOS, altered liver function (0.2 - 1.0%) The following adverse event occurred in less than 1% of patients: Jaundice
Immune system disorders	Allergic reactions (0.2 - 1.0%)
Infections and infestations	Genitourinary infection (0.2 - 1.0%)
Musculoskeletal and connective tissue disorders	Backache (2%) Limb pain (4%) Leg cramps, arthralgia (1-5%) The following adverse events occurred in less than 1% of patients: Osteoporosis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	The following adverse events occurred in less than 1% of patients: Breast cancer, cervical cancer
Nervous system disorders	Headache (17%) Dizziness (6%) Somnolence or drowsiness, paraesthesia, sensory disturbances (0.2 - 1.0%) The following adverse events occurred in less than 1% of patients: Syncope, convulsions, paralysis, facial palsy
Pregnancy, puerperium and perinatal conditions	The following adverse events occurred in less than 1% of patients: Unexpected pregnancy, sensation of pregnancy
Psychiatric disorders	Nervousness (12%) Decreased libido (6%) Depression (2%) Anorgasmia (1-5%) Insomnia (0.2 - 1.0%) The following adverse event occurred in less than 1% of patients: Increased libido
Renal and urinary disorders	Dysuria, urinary frequency (0.2 - 1.0%)
Reproductive system and breast disorders	Breast swelling/tenderness (3%) Vaginal discharge (3%) Leukorrhoea (1-5%) Pelvic pain (1-5%) Vaginitis (1-5%) Dysmenorrhea (2%) Pruritus vulvae (1%) Galactorrhea, bleeding requiring D&C, dyspareunia (0.2 - 1.0%) The following adverse events occurred in less than 1% of patients: Changes in breast size, breast lumps or nipple bleeding, prevention of lactation, vaginal cysts, lack of return to fertility, uterine hyperplasia
Respiratory, thoracic and mediastinal disorders	Dyspnea (0.2 - 1.0%) The following adverse events occurred in less than 1% of patients: Asthma, hoarseness, pulmonary embolus
Skin and subcutaneous tissue disorders	Acne, alopecia, rash (1%) Hirsutism, pruritus (0.2 - 1%) Hives (0.2 - 1.0%)

SYSTEM ORGAN CLASS	EVENT
	The following adverse events occurred in less than 1% of patients: Melasma, chloasma, scleroderma, excessive sweating, body odour, dry skin
Vascular disorders	Hot flashes (1%) The following adverse events occurred in less than 1% of patients: Varicose veins, thrombophlebitis, deep vein thrombosis

DEPO-PROVERA-SC

Drug-related adverse events were reported for 39.4% (805/2043) of subjects in the All MPA-SC group. The most frequently reported drug-related adverse events (preferred terms) for the MPA-SC group were intermenstrual bleeding (7.0%, 143/2043), weight increased (6.7%, 136/2043) and amenorrhea NOS (6.3%, 129/2043).

Serious adverse events were infrequently reported. Serious events were reported for 1.7% (36/2053) of subjects with safety data receiving MPA-SC. The only serious events reported for more than 1 subject were abdominal pain, appendicitis, road traffic accident, depression, suicide attempt and uterine hemorrhage (reported for 2 or 3 subjects each).

The most frequently reported (ie, at least 1% of subjects) adverse events leading to discontinuation in subjects treated with MPA-SC were increased weight (2.0%, 40/2043), intermenstrual bleeding (1.2%, 24/2043), decreased libido (1.1%, 22/2043), and acne (1.0%, 20/2043).

Table 5 displays adverse events that were reported in at least 1% of the subjects treated with MPA-SC. Both treatment groups in Study 267BMD are presented for comparison.

Table 5. Treatment-Emergent Adverse Events Reported in ≥1%* of Subjects (ITT Population)

System/Organ Class Preferred Term‡	All MPA-SC N = 2053		267BMD MPA-SC N = 266†		267BMD MPA-IM N = 268	
	n	%	n	%	n	%
Gastrointestinal disorders						
Abdominal pain NOS	41	2.0	6	2.3	16	6.0
Nausea	54	2.6	15	5.7	24	9.0
General disorders and administration site conditions						
Injection site reactions **	124	6.0	24	9.0	1	0.4
Fatigue	46	2.3	10	3.8	4	1.5
Irritability	23	1.1	6	2.3	4	1.5
Infections and infestations						
Vaginitis	29	1.4	11	4.2	11	4.1
Investigations						
Smear cervix abnormal	38	1.9	9	3.4	14	5.3
Metabolism and nutrition						
Weight increase	140	6.9	33	12.5	39	14.7
Musculoskeletal, connective tissue, and bone disorders						
Back pain	49	2.4	13	4.9	13	4.9
Pain in limb	24	1.2	4	1.5	8	3.0

Table 5. Treatment-Emergent Adverse Events Reported in ≥1%* of Subjects (ITT Population)

System/Organ Class Preferred Term‡	All MPA-SC N = 2053		267BMD MPA-SC N = 266†		267BMD MPA-IM N = 268	
	n	%	n	%	n	%
Nervous system disorders						
Headache NOS	173	8.5	35	13.3	33	12.4
Dizziness (excluding vertigo)	27	1.3	7	2.7	4	1.5
Psychiatric disorders						
Anxiety NEC	21	1.0	10	3.8	7	2.6
Insomnia NEC	32	1.6	13	4.9	8	3.0
Depression NEC	45	2.2	14	5.3	13	4.9
Libido decreased	63	3.1	8	3.0	16	6.0
Reproductive system and breast disorders						
Amenorrhea NOS	130	6.4	2	0.8	5	1.9
Breast pain	27	1.3	2	0.8	3	1.1
Intermenstrual bleeding	145	7.1	15	5.7	15	5.6
Menometrorrhagia	51	2.5	9	3.4	10	3.8
Menorrhagia	33	1.6	0	0.0	3	1.1
Dysmenorrhoea	23	1.1	11	4.2	4	1.5
Skin and subcutaneous tissue disorders						
Acne NOS	67	3.3	20	7.6	20	7.5

∗ The 1% cut-point was based on all MPA-SC-treated subjects. Both treatment groups in Study 267BMD are included as a comparison.
† These subjects are also included in the all MPA-SC column.
‡ MedDRA version 2.3
Note that data were not available for 10 subjects in the DMPA-SC group (including 3 in Study 267BMD) and for 2 subjects in the DMPA-IM group.
Abbreviations: ITT = intent-to-treat, NEC = not elsewhere classified, NOS = not otherwise specified
** such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy or injection site reaction general

Less Common Clinical Trial Adverse Drug Reactions (<1%) (DEPO-PROVERA-SC)

Ear and labyrinth disorders: vertigo NEC

Gastrointestinal disorders: abdominal distension

Investigations: abnormal liver enzymes

Metabolism and nutrition: appetite decreased, appetite increased, fluid retention

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: migraine NOS

Psychiatric disorders: anorgasmia, emotional disturbances NOS, mood disorder NOS

Skin and subcutaneous tissue disorders: hirsutism, chloasma, dermatitis, ecchymosis, rash, alopecia

Reproductive system and breast disorders: breast tenderness, vaginal discharge, vulvovaginal dryness, change in breast size, dyspareunia, ovarian cyst, pelvic pain NOS, premenstrual syndrome

Vascular disorders hot flushes NOS, hypertension, varicose veins

Post-Market Adverse Drug Reactions (DEPO-PROVERA)

In post-marketing experience, there have been cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA. Patient age ranged from 16 years to 48 years. Other adverse events reported during post-marketing experience, regardless of causality and frequency, are listed below. It should be noted that the nature of post-marketing surveillance makes it difficult to determine if a reported event was actually caused by DEPO-PROVERA.

Blood and lymphatic system disorders: hemolytic anemia, hemorrhagic disorder, sickle cell crisis, splenic infarction, thrombocytopenia, thrombotic thrombocytopenic purpura

Cardiac disorders: bradycardia, myocardial infarction, palpitations, pericarditis, possible exacerbation of prolonged QT interval syndrome (with fatal outcome), supraventricular tachycardia

Congenital and familial/genetic disorders: acute porphyria, in cases of failure of contraception: Trisomy 21, Trisomy 16, Turner's syndrome

Ear and labyrinth disorders: change in hearing, tinnitus, vertigo

Endocrine disorders: adrenal dysfunction NOS, Cushingoid, estrogen deficiency, hyperthyroidism, hypoglycemia, hypopituitarism, hypothyroidism, thyroiditis

Eye disorders: macular edema, optic ischemic neuropathy, optic neuritis, papilloedema, ptosis, retinal vein occlusion, vision loss, visual changes

Gastrointestinal disorders: acute pancreatitis, dysphagia, intestinal infarction, mouth ulceration, oral mucosal blistering, salivary gland enlargement

General disorders and administration site conditions: fatigue, injection site reactions (including swelling, rash, ulcer, necrosis, edema, infection, abscess), malaise, sudden infant death syndrome (exposure-in utero)

Hepatobiliary disorders: Cholangitis, cholelithiasis, gallbladder disorder, hepatitis, hepatomegaly, obstructive jaundice, hepatic failure (with fatal outcome)

Injury, poisoning, and procedural complications: exposure in utero: abnormal genitalia, anencephaly, cleft palate, congenital adenomatoid malformation, congenital diaphragmatic hernia, congenital heart defects, congenital megacolon, ear malformation NOS, esophageal atresia, hydrocephalus, hypospadias, limb deformity, microcephaly, polydactyly, single umbilical artery, skull malformation, spina bifida, Talipes, tracheoesophageal fistula

Immune system disorders: anaphylactic reaction (with fatal outcome in rare cases), hypersensitivity

Infections and infestations: salpingitis, sepsis, vulval abscess

Investigations: coagulation Factor X decreased, decreased blood folate, decreased blood pressure, decreased estrogen, decreased testosterone, elevated blood creatinine, hypernatremia, hypokalemia, increased alanine aminotransferase, increased alkaline phosphatase, increased blood pressure, increased creatine phosphokinase, increased triglycerides, leukocytosis, weight decreased

Metabolism and nutrition disorders: cachexia, excessive thirst

Musculoskeletal, connective tissue and bone disorders: joint swelling, muscle weakness, myalgia, osteonecrosis

Neoplasms benign, malignant and unspecified: acute leukemia, benign breast neoplasm, benign hydatidiform mole, fibroadenoma of breast, Hodgkin's disease, kidney neoplasm, malignant melanoma, meningioma, neurofibroma, ovarian cancer, squamous cell carcinoma of the cervix, uterine leiomyoma

Nervous system disorders: amnesia, anosmia, ataxia, balance disorder, benign intracranial hypertension, cerebral hemorrhage, cerebral ischemia/infarct, cerebral venous thrombosis, cerebrovascular accident, confusion, dysarthria, dysgeusia, memory loss, migraine, myoclonus, Parkinsonism, seizures, speech disorder, stroke (with fatal outcome), third nerve palsy, transient ischemic attack, tremor

Pregnancy, peurperium and perinatal conditions: exposure-in-utero: antepartum hemorrhage, blighted ovum, ectopic pregnancy, fetal hydrops, intrauterine growth retardation, missed abortion, polyhydramnios, prematurity, spontaneous abortion, stillbirth

Psychiatric disorders: acute psychosis, agitation, anxiety, attention deficit/hyperactivity disorder, dysphemia, eating disorder, irritability, mood swings, paranoia, suicidality

Renal and urinary disorders: interstitial nephritis, nephrolithiasis, nephrotic syndrome, proteinuria, renal infarct, urinary retention

Reproductive system and breast disorders: cervical dysplasia, fibrocystic breast disease, menorrhagia, ovarian cyst, premature menopause, uterine cyst, vaginal dysplasia, vaginal mucosal blistering

Respiratory, thoracic and mediastinal disorders: acute respiratory distress syndrome, bronchospasm, epistaxis, laryngeal edema, laryngospasm, oropharyngeal swelling

Skin and subcutaneous tissue disorders: angioedema, erythema multiforme, erythema nodosum, facial edema, porphyria aggravated

Vascular disorders: arterial thrombosis, embolism, Henoch-Schonlein purpura, postural hypotension, venous thrombosis (including rare cases with fatal outcome)

DRUG INTERACTIONS

Overview

Aminoglutethimide: Aminoglutethimide administered concomitantly with DEPO-PROVERA or DEPO-PROVERA-SC (medroxyprogesterone acetate) may significantly depress the serum concentration of medroxyprogesterone acetate. Users of DEPO-PROVERA should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Rifampin: Rifampin can increase the metabolism of exogenously administered progestational agents. Norethindrone has specifically been affected; a reduction of plasma concentrations has occurred. The extent to which rifampin may alter the metabolism of other progestogens remains to be determined; the possibility of an interaction should be considered.

Drug-Drug Interactions

Medroxyprogesterone acetate (MPA) is metabolized in-vitro primarily by hydroxylation via the CYP3A4.[52, 53]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.

The results of one study indicated that intramuscularly administered medroxyprogesterone acetate may induce or activate the CYP3A4 enzyme system, leading to an increased metabolism of many CYP3A4 substrates.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Certain endocrine and possibly liver function tests may be affected by treatment with DEPO-PROVERA or DEPO-PROVERA-SC. Therefore, if such tests are abnormal in a woman taking DEPO-PROVERA or DEPO-PROVERA-SC, it is recommended that they be repeated 6 to 12 months after the drug has been withdrawn.

The clinical chemist or pathologist should be advised of progestogen therapy when a woman's blood or tissue specimens are submitted for laboratory diagnosis or biochemical analysis.

The following laboratory tests may be affected by the use of DEPO-PROVERA or DEPO-PROVERA-SC:

(a) Gonadotropin levels - inhibition of the midcycle LH surge

(b) Plasma progesterone levels - inhibition of ovulation and thus the postovulatory rise of progesterone
(c) Plasma estrogen levels - do not exceed early-to-mid-proliferative phase levels
(d) Plasma cortisol levels - not significantly affected by the dose used for contraception
(e) Glucose tolerance test - occasionally some degree of glucose intolerance may develop
(f) Plasma lipid concentrations - decrease in high density lipoprotein cholesterol (HDL-C) in some studies. The clinical relevance of this has yet to be determined
(g) Urinary pregnanediol levels (Note: DEPO-PROVERA does not interfere with the assay of human chorionic gonadotropin (HCG) either chemically or pharmacologically).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Conception Control (prevention of pregnancy):

DEPO-PROVERA Intramuscular formulation:
The recommended dose for contraception is 150 mg of DEPO-PROVERA (medroxyprogesterone acetate) every 3 months, administered by deep intramuscular injection.

DEPO-PROVERA-SC Subcutaneous formulation:
The recommended dose for contraception is a pre-filled syringe of DEPO-PROVERA-SC (104 mg/0.65 mL). DEPO-PROVERA-SC injection must be given by subcutaneous injection into the anterior thigh or abdomen, every 12 – 14 weeks (3 months). Dosage does not need to be adjusted for body weight, (see **ACTION AND CLINICAL PHARMACOLOGY**). The MPA-SC suspension is not formulated for intramuscular injection.

To increase assurance that the woman is not pregnant at the time of the first administration, it is recommended that this injection be given **only** within the 5 five days of the onset of a normal menstrual period or, **only** within the first 5 days post-partum if not breast-feeding. If the woman has chosen to breast-feed, discuss the risks of pregnancy and possible risks of DEPO-PROVERA or DEPO-PROVERA-SC to determine the most appropriate course of action for the individual woman (see **WARNINGS AND PRECAUTIONS**).

If administered within the first 5 days after the onset of a normal menstrual period, DEPO-PROVERA or DEPO-PROVERA-SC is effective from the day of injection. When DEPO-PROVERA or DEPO-PROVERA-SC is given later in the menstrual cycle it may not be effective for the first 3 to 4 weeks after the injection and another method of contraception (non-hormonal) should be used during this time.

After miscarriage or first trimester therapeutic abortion, the injection is normally given within 5 days of the procedure and no extra precautions are required. After a late (second trimester) abortion, some further delay is recommended to reduce the risk of heavy and prolonged bleeding, therefore, the first injection should not be given until 4 weeks after the procedure.

The woman must return every 10 to 13 weeks for a repeat intramuscular injection to maintain contraceptive effectiveness. **Intervals between intramuscular injections must not exceed 13 weeks (3 months).**

When switching from other contraceptive methods, (MPA intramuscular or subcutaneous) 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 should have their first injection of MPA within 7 days after taking their last active pill).

Endometriosis:
The recommended dose of DEPO-PROVERA is 50 mg weekly or 100 mg every 2 weeks intramuscularly for at least 6 months. It should be noted that return of ovulation may be delayed following this therapy due to the depot properties of the drug **(**see **WARNINGS AND PRECAUTIONS).**

Use in Children:

DEPO-PROVERA or DEPO-PROVERA-SC should not be used before menarche (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**).

See **WARNINGS AND PRECAUTIONS,** Loss of Bone Mineral Density for available data for adolescent females (12-18 years).

Missed Dose
DEPO-PROVERA
If an injection is not given within 13 weeks a pregnancy test should be done before any further treatment with DEPO-PROVERA.

DEPO-PROVERA-SC
If more than 14 weeks elapse since the last subcutaneous injection, pregnancy should be ruled out before administering the next subcutaneous injection.

Administration

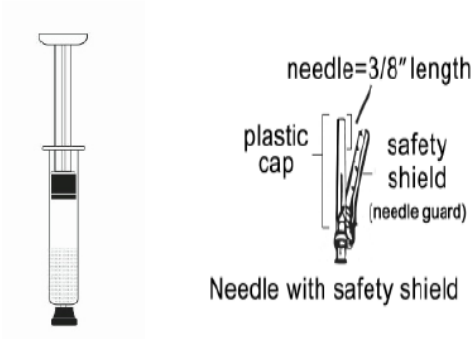
DEPO-PROVERA is intended for **INTRAMUSCULAR ADMINISTRATION ONLY**.

DEPO-PROVERA-SC is intended for **SUBCUTANEOUS ADMINISTRATION ONLY**. Immediately before use, the sterile aqueous suspension should be vigorously shaken to assure that the dose being administered represents a uniform suspension.

DEPO-PROVERA-SC is supplied in a pre-filled syringe (see Figure 3).

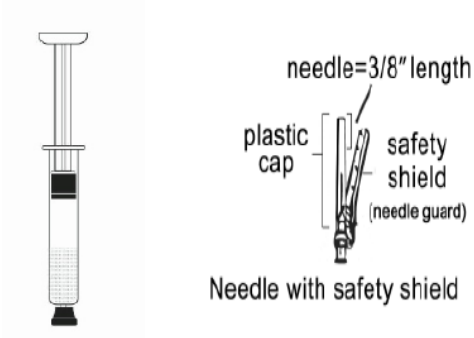
DEPO-PROVERA-SC should be administered by a healthcare professional who has been trained in administering subcutaneous injections.

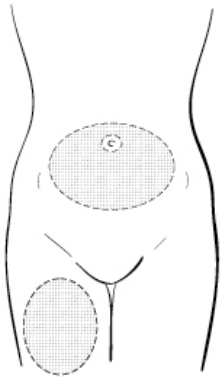
Figure 3: Pre-filled syringe

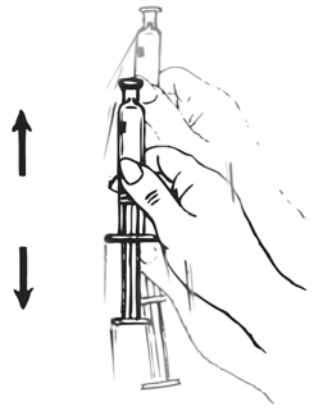
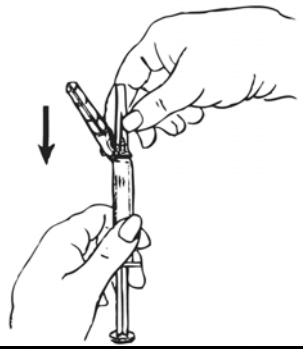


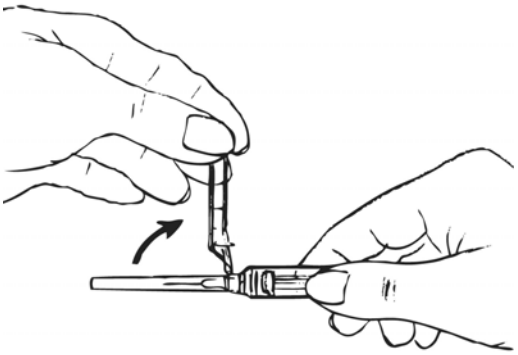
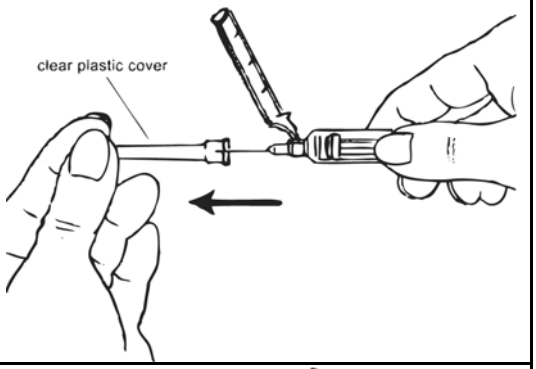
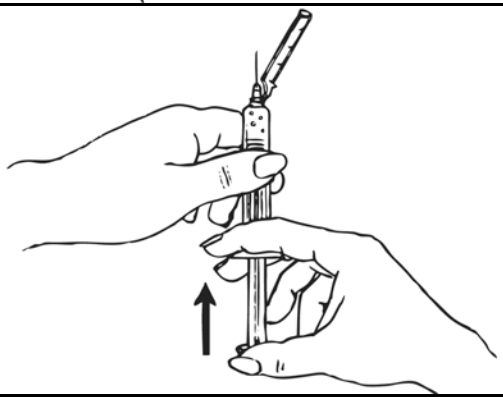
Instructions for Administration of DEPO-PROVERA-SC (pre-filled syringe) for Subcutaneous Use

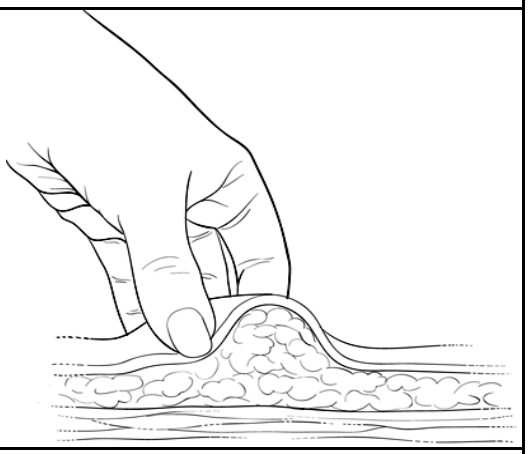
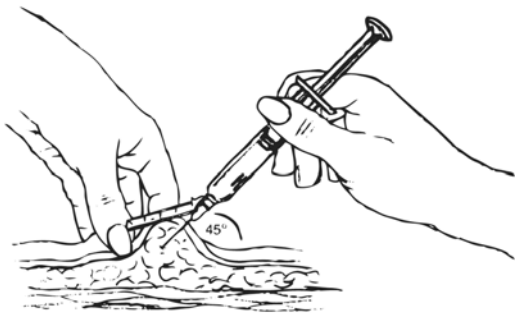
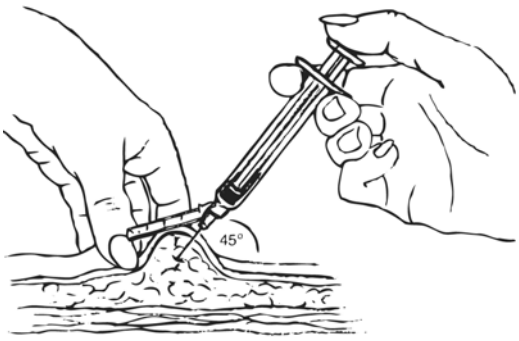
Please read these instructions carefully. It is very important that the entire dose of DEPO-PROVERA-SC is given.

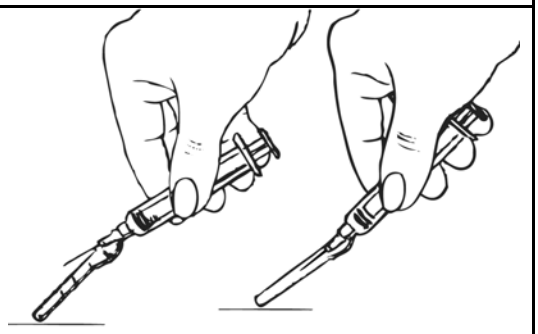
Getting ready Ensure that the medication is at room temperature. Make sure the following components are available.	
DEPO-PROVERA-SC (pre-filled syringe), as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.	

Step 1: Choosing and preparing the injection area. Choose the injection area. Avoid bony areas and the umbilicus. See shaded areas. Upper thigh & Abdomen.	
Use an alcohol pad to wipe the skin in the injection area you have chosen. Allow the skin to dry.	

Step 2: Syringe preparation	
Carefully remove the needle and syringe from the packaging. Hold the syringe firmly by the barrel, with the barrel pointing upward. • **Shake it forcefully for at least 1 minute** to thoroughly mix the medication	
Hold the syringe barrel firmly. • **Unscrew the protective cap** from the tip of the syringe barrel	
Hold the syringe barrel firmly. • Attach the needle to the barrel of the syringe by pushing down firmly with a slight twist	

Move the safety shield away from the needle and toward the syringe barrel. The safety shield will remain in an open 45 to 90 degree position	
While holding the syringe barrel firmly, **remove the plastic cover** from the needle without twisting, ensuring the needle is still firmly attached to the syringe	
While holding the syringe with the needle pointing upward, **gently push in the plunger** until the medicine is up to the top of the syringe. There should be no air within the barrel	

Step 3: Injecting the dose.	
Gently grasp and squeeze a large area of skin in the chosen injection area between the thumb and forefinger, pulling it away from the body.	
Insert the needle at a 45 degree angle so that most of the needle is in the fatty tissue. • The plastic hub of the needle should be nearly or almost touching the skin	
Inject the medication slowly until the syringe is empty. • It is important that the entire dose of **DEPO-PROVERA-SC** is given • This should take about 5–7 seconds	

Step 4: Disposing the needle and syringe	
After completing the injection, remove the needle from the skin and activate the safety shield. Position shield about 40°- 45°. With a firm quick motion, press down against a flat surface until a click is heard or felt **If uncertain that the safety shield is fully engaged, repeat this step**.	

OVERDOSAGE

Overdosage may result in a period of amenorrhea of a variable length and may be followed by irregular menses for several cycles. Very high doses of DEPO-PROVERA (500 mg daily or more) have been associated with corticoid-like activity and with Cushingoid symptoms (e.g. moon facies and blood pressure elevation). There is no known therapy for overdosage.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

DEPO-PROVERA or DEPO-PROVERA-SC (medroxyprogesterone acetate) is a long-acting progestational steroid (progestogen) derived from a natural source (soybeans). Its long duration of action is a result of slow absorption from the injection site. DEPO-PROVERA does not contain estrogen.

For conception control, DEPO-PROVERA or DEPO-PROVERA-SCinhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation, and results in endometrial thinning. Additional progestational effects that may contribute to the contraceptive effectiveness of DEPO-PROVERA or DEPO-PROVERA-SC include the transformation and maintenance of an endometrium hostile to implantation, and thickening of cervical mucus making sperm penetration of the cervix more difficult.

DEPO-PROVERA or DEPO-PROVERA-SC administered parenterally to women with adequate endogenous estrogen transforms proliferative endometrium into secretory endometrium.

Endometriosis is an estrogen-dependent disorder in women of reproductive age that is characterized by the presence of endometrial-like tissue (glands and stoma) outside the uterine lining. The putative mechanisms of action of DEPO-PROVERA or DEPO-PROVERA-SC in the treatment of endometriosis is by inhibition of gonadotropin production, induction of decidualization followed by atrophy of endometriotic implants, prevention of follicular maturation and ovulation and decrease in circulating estrogen levels.

Pharmacokinetics

Table 6. Summary **of medroxyprogesterone acetate suspension for injection's pharmacokinetic parameters in an adult women population**

	C_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$	Clearance	Volume of distribution
Single 150 mg I.M.	1-7 ng/mL	≈ 1000	NA*	1600-4000 litres/day	20 ± 3 litres

* not available

Table 7. Pharmacokinetic Parameters of MPA after a Single Subcutaneous Injection of DEPO-PROVERA-SC in Healthy Women (n = 42)

	C_{max} (ng/mL)	$t_{½}$ (day)	$AUC_{0-\infty}$ (ng·day/mL)	AUC_{0-91} (ng·day/mL)	T_{max} (day)	C_{91} (ng/mL)	CL_{91} (ng/mL)
Mean	1.56	43	92.84	66.98	8.8	0.402	0.402
Min	0.53	16	31.36	20.63	2.0	0.133	0.133
Max	3.08	114	162.29	139.79	80.0	0.733	0.733

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; C_{91} = serum concentration at 91 days; AUC_{0-91} and $AUC_{0-\infty}$ = area under the concentration-time curve over 91 days or infinity, respectively; t½ = terminal half-life

Absorption: Following intramuscular administration, MPA is slowly released from the injection site, resulting in low, but persistent levels of drug and drug-related materials in the circulation. On average, the time required to obtain a maximum concentration of MPA in the circulation is between 4 and 20 days. Following a single 150 mg IM dose of DEPO-PROVERA, medroxyprogesterone acetate (MPA) concentrations, measured by an extracted radioimmunoassay procedure, increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL.

Circulating levels of MPA can be detected for as long as 7 to 9 months. Increasing the injection volume of medroxyprogesterone acetate produces an increased rate of absorption and higher serum levels; however, extent of absorption is not affected.

Following subcutaneous administration, MPA absorption from the subcutaneous injection site to achieve therapeutic levels is relatively prompt. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single subcutaneous injection.

DEPO-PROVERA-SC (MPA subcutaneous) was administered into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution: Medroxyprogesterone acetate is approximately 90 to 95 percent protein bound. Volume of distribution is reported as 20 ± 3 litres. It crosses the blood-brain barrier and is secreted in breast milk.

Plasma protein binding of DEPO-PROVERA-SC (MPA subcutaneous) averages 86%. MPA binding occurs primarily to serum albumin; no binding of MPA occurs with SHBG.

Metabolism: The principal metabolite of medroxyprogesterone acetate that has been identified is a 6α-methyl-6β, 17α, 21-trihydroxy-4-pregnene-3, 20-dione-17-acetate, which is excreted in the urine. Numerous other metabolites of medroxyprogesterone acetate have been reported; however, these have not been well quantified. Metabolism may be influenced by the route of administration as well as the physical state of the drug.

DEPO-PROVERA-SC (MPA subcutaneous) is extensively metabolized in the liver.

Excretion: The terminal half-life of MPA is approximately 30 to 60 hours. The elimination half-life following intramuscular administration is approximately 6 weeks, reflecting the prolonged absorption of the drug from the intramuscular injection site. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 to 200 days following injection. Plasma clearance is reported as approximately 1600-4000 litres per day. Medroxyprogesterone acetate (as the glucuronide conjugate) is primarily excreted in the feces, via biliary secretion.

Residual MPA concentrations at the end of the dosing interval (3 months) of DEPO-PROVERA-SC (MPA subcutaneous) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after subcutaneous administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Special Populations and Conditions

Hepatic Insufficiency: The effect of hepatic disease on the pharmacokinetics of DEPO-PROVERA is unknown. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolized in patients with severe liver insufficiency, (**see CONTRAINDICATIONS**).

Renal Insufficiency: The effect of renal disease on the pharmacokinetics of DEPO-PROVERA is unknown.

Race:
There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after subcutaneous administration of DEPO-PROVERA-SC among women of all ethnic backgrounds studied. The pharmacokinetics/dynamics of MPA has been evaluated in Asian women in a separate study.

Effect of Body Weight:
No dosage adjustment of MPA subcutaneous is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n = 42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m^2). The $AUC_{0\text{-}91}$ values for MPA were 68.5, 74.8, and 61.8 ng -day/mL in women with BMI categories of ≤25 kg/m^2, >25 to ≤30 kg/m^2, and >30 kg/m^2, respectively. The mean MPA C_{max} was 1.65 ng/mL in women with BMI ≤25 kg/m^2, 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m^2, and 1.40 ng/mL in women with BMI > 30 kg/m^2, respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

STORAGE AND STABILITY

DEPO-PROVERA

Protect from freezing. Store upright at controlled room temperature 15° to 30°C. Shake well before using. Keep out of reach of children.

DEPO-PROVERA-SC

Protect from freezing. Store at controlled room temperature 15° to 25°C. Shake well before using. Keep out of reach of children. Do not bend.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

DEPO-PROVERA

Each mL of DEPO-PROVERA contains:

Ingredients (mg)	50 mg/mL	150 mg/mL
Medroxyprogesterone acetate	50	150
Polyethylene Glycol 3350	28.8	28.9
Polysorbate 80	1.9	2.41
Sodium Chloride	8.6	8.68
Methylparaben	1.3	1.37
Propylparaben	0.14	0.15
Water for injection, Sodium Hydroxide, Hydrochloric Acid	q.s.	q.s.

DEPO-PROVERA (medroxyprogesterone acetate) is supplied in 2 strengths.

50 mg/mL	5 mL vials	Single use only
150 mg/mL	1 mL vials	1 x 1 mL vials; 5 x 1 mL vials, 25 x 1 mL vials

DEPO-PROVERA-SC

Composition:
Each 0.65 mL of DEPO-PROVERA-SC contains:

Ingredients (mg)	104mg/0.65mL
Medroxyprogesterone acetate	104
Methyl Parahydroxybenzoate / Methylparaben	1.040
Propyl Parahydroxybenzoate / Propylparaben	0.098
Sodium Chloride	5.200
Macrogol/Polyethylene Glycol, 3350	18.688
Polysorbate 80	1.950
Monobasic Sodium Phosphate• 1 H_2O	0.451
Disodium Phosphate Dodecahydrate/ Dibasic Sodium Phosphate • 12 H_2O	0.382
Methionine	0.975
Povidone, K17 PF	3.250
Sodium Hydroxide, Hydrochloric Acid	q.s.
Water for injection,	q.s.

DEPO-PROVERA-SC (medroxyprogesterone acetate) is supplied in 1 strength.

104 mg/0.65mL	0.65 mL Pre-filled glass syringe	Single use only

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

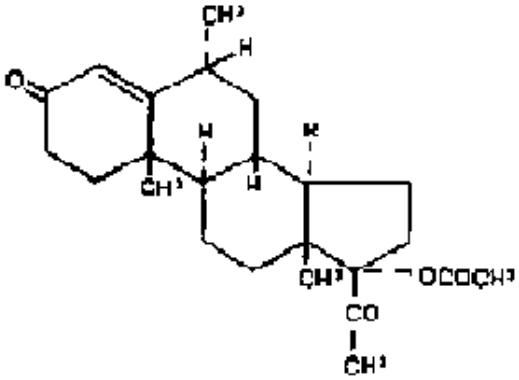
Proper name: medroxyprogesterone acetate

Chemical name: (1) Pregn-4-ene-3,20 dione,17-(acetyloxy)-6-methyl-,(6α)-;

(2) 17-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate

Molecular formula and molecular mass: $C_{24}H_{34}O_4$ 386.53

Structural formula:



Physicochemical properties: Medroxyprogesterone acetate is a white to off-white, odourless crystalline powder, stable in air. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water. The melting point is between 200 and 210°C. The c log P is 1.467.

CLINICAL TRIALS

DEPO-PROVERA

Conception control

The contraceptive efficacy, safety and acceptability of DEPO-PROVERA (medroxyprogesterone acetate) given as a single intramuscular injection of 150 mg every 90 days has been evaluated in a multicentre study conducted by 54 investigators in the United States.

Protocol
A baseline interview, pelvic examination, weight measurement, blood pressure reading, laboratory study and Papanicolaou smear were carried out. The initial injection of DEPO-PROVERA was given toward the end of, or on the day immediately following, a menstrual period in all subjects. Monthly calendar cards were issued on which to record menstrual periods, instructions were given detailing possible side effects (amenorrhea, irregular bleeding), and appointments were made for follow-up and repeat injections in 3 months. At monthly time intervals, interviews were conducted and monthly calendar cards were collected. At 3-month intervals, subjects reported for repeat injections and body weight and laboratory test performance. At this time interviews were again conducted as to acceptance of therapy, side effects, and signs of pregnancy. Follow-up pelvic examinations, Pap smears and blood pressure measurements were performed 1 year after first injection (at the time of the fifth injection).

Number of Patients and Study Duration
Fifty-four investigators enrolled 3,905 patients into the study. Table 8 contains the number of patients completing at least the stated study month. For example 2,253 patients were in the study for 12 months or more; 827 patients were in the study for 36 months or more. The median study duration was 13 months. The ten-percentile was 3 months, the ninety-percentile 51 months, the minimum 1 month and the maximum 84 months. The total number of patient-months of experience on the drug was 82,384.

TABLE 8
DEPO-PROVERA EVERY 90 DAYS
NUMBER OF PATIENTS COMPLETING AT LEAST STATED STUDY MONTH

Study Month	No. of Patients	Study Month	No. of Patients	Study Month	No. of Patients
0 - 1	3905	29	1068	57	305
2	3670	30	1037	58	285
3	3571	31	984	59	267
4	3294	32	950	60	263
5	3084	33	927	61	250
6	3004	34	887	62	238
7	2792	35	857	63	227
8	2634	36	827	64	215
9	2576	37	765	65	206
10	2419	38	735	66	201
11	2288	39	622	67	199
12	2253	40	685	68	190
13	2030	41	673	69	184
14	1915	42	664	70	182
15	1872	43	606	71	174
16	1776	44	588	72	157
17	1704	45	573	73	143
18	1659	46	525	74	129
19	1567	47	493	75	118
20	1514	48	474	76	110
21	1485	49	436	77	97
22	1422	50	417	78	91
23	1367	51	412	79	77
24	1344	52	375	80	67

TABLE 8					
DEPO-PROVERA EVERY 90 DAYS NUMBER OF PATIENTS COMPLETING AT LEAST STATED STUDY MONTH					
Study Month	**No. of Patients**	**Study Month**	**No. of Patients**	**Study Month**	**No. of Patients**
25	1251	53	358	81	49
26	1200	54	350	82	23
27	1180	55	326	83	3
28	1116	56	316	84	1
Total Patient-Months Experience:					82,384

Patient Description

The median age of the patients was 26 years; 11.3 percent of the patients were age 19 years or less; 85.7 percent were age 20 through 39 years; 3.0 percent were age 40 years or greater.

Caucasians accounted for 54.7 percent of the patient group. The median number of months since last delivery or miscarriage was 6. The median gravida was 3. The median para was 3. 65.3 percent of the patients were abortus zero.

Efficacy Results

In total, 15 (0.38%) of the 3,905 patients dropped out of the study due to method failure (pregnancy). The 12-month cumulative dropout rate (dropouts per 100 women - life table technique) due to pregnancy was 0.32 with a standard error of 0.11.

The 12-month pregnancy rate, or failure rate, as calculated by the life table technique is 0.32 per 100 women. The 24-month failure rate is 0.44 per 100 women and the 36-month failure rate is 0.75 per 100 women. Table 9 summarizes cumulative dropout rates due to pregnancy according to the months of the study in which a patient dropped out due to method failure.

TABLE 9					
DEPO-PROVERA EVERY 90 DAYS DROPOUTS/FAILURES (PREGNANCY)					
Month	**No. of Patients Entering Month**	**Dropouts**	**Interval Rate**	**Cumulative Rate**	**Standard Error of Cumulative Rate**
3	3571	1	0.0003	0.0003	0.0003
4	3294	2	0.0006	0.0009	0.0005
6	3004	2	0.0007	0.0016	0.0007
7	2792	1	0.0004	0.0019	0.0008
9	2576	1	0.0004	0.0023	0.0009
10	2419	1	0.0004	0.0027	0.0010
12	2253	1	0.0004	0.0032	0.0011
15	1872	1	0.0005	0.0037	0.0012
23	1367	1	0.0007	0.0044	0.0014
29	1068	1	0.0009	0.0053	0.0017
33	927	2	0.0022	0.0075	0.0023
39	722	1	0.0014	0.0089	0.0026

Dropouts

Table 10 contains frequency distribution of dropouts by dropout reason. Listed are only those reasons found common to greater than 1.0 percent of the women entering the study.

TABLE 10 DEPO-PROVERA EVERY 90 DAYS-REASONS FOR DROPOUT		
Reasons	# Women	% of Total Women(n=3905)
Study completed	1086	27.81
Lost to follow-up	774	19.82
Husband objects - inconvenient to come to clinic, to attempt to conceive, objects to expense, personal reasons, no longer requires contraception	568	14.55
Bleeding	326	8.35
Side effects (unspecified)	245	6.27
Moved away	215	5.51
Advice of clinic or private physician	126	3.23
Amenorrhea	86	2.20
Weight gain, excessive	78	2.00
Unknown	68	1.74
Hysterectomy, tubal ligation	61	1.56
Headache	39	1.00

Continuation Rate

The expected continuation rate for a specific point in time may be calculated by subtracting the dropout rate for all reasons (except protocol completed for the specific point in time), from 100. The life table expected continuation rates for selected points in time are as follows:

Month	Continuation Rate	Standard Error
12	56.13%	0.80%
24	38.82%	0.81%
36	28.97%	0.78%
48	23.50%	0.77%
60	19.71%	0.79%
72	16.71%	0.83%

Conclusion

DEPO-PROVERA given as a single intramuscular injection of 150 mg every 90 days has been assessed overall as a safe and effective method of contraception and is well tolerated by the majority of patients.

The following table shows the reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant during the first year of use.

DEPO-PROVERA Sterile Aqueous Suspension Reported Pregnancies per 100 Women per Year			
Method		**Lowest expected**	**Typical**
DEPO-PROVERA		**0.3**	**0.3**
Female sterilization		0.2	0.4
Male sterilization		0.1	0.15
Oral Contraceptives (the pill)		0.1- 0.5	3
IUD	Copper T 380A	0.8	3
Condom		2	12
Diaphragm		6	18
Sponge	women who have not had any children	6	18
	women who have had children	9	28
Cap		6	18
Withdrawal		4	18
Periodic abstinence		1-9	20
Spermicides		3	21
Chance (no birth control)		85	85

DEPO-PROVERA-SC:

Study demographics and trial design

The clinical program for contraception consisted of 3 Phase 3 studies (267, 269, and 267BMD). Studies 267 and 269 were open-label, noncomparative, multinational, multicenter, 1-year studies to evaluate the efficacy and safety of and subject satisfaction with MPA-SC when administered at a dose of 104 mg every 3 months to women in America (Study 267) or women in Europe and Asia (Study 269). Study 267BMD is a substudy of Study 267; this portion of the study is an evaluator blinded, 3-year study to compare the effects of MPA-SC (104 mg administered every 3 months) on bone mineral density (BMD) with those of MPA-IM (150 mg administered every 3 months).

The primary efficacy objective was to assess contraceptive efficacy of MPA-IM and MPA-SC for up to 3 years with 1, 2, and 3-year analysis timepoints.

Patient Description

The 3 Phase 3 studies enrolled nonpregnant, sexually active women of childbearing potential aged 18 to 49 years (studies 267 and 269) or 18 to 35 years (Study 267BMD) who desired long term contraception and who were willing to rely on MPA for contraception for the duration of the study. Eligible subjects were those who had not received oral contraceptives for the 2-month period before enrollment and who had been menstruating regularly (with an average cycle length of 25 to 35 days) during the 3-month period before enrollment. Women who had been treated with oral contraceptives, contraceptive implants, or hormone medicated intrauterine devices in the 2-month period before enrollment or who had been treated with MPA-IM in the 10-month period before enrollment were ineligible. The mean age was 30.0 years for all MPA-SC-treated subjects. Most (82.4%) of the subjects were Caucasian. Mean BMI was 24.3 kg/m^2 for all MPA-SC-treated subjects; it was higher for subjects in both the MPA-SC and MPA-IM treatment groups of

Study 267BMD. Demographic characteristics were similar between the MPA-SC and MPA-IM treatment groups in Study 267BMD.

A total of 2321 women were enrolled in and received at least 1 dose of MPA-SC in the 3 Phase 3 trials (studies 267, 269, and 267BMD); 1503 (73.2%) completed 1 year of treatment with MPA-SC. The primary reason for discontinuation from the study across all studies was withdrawal of consent, followed by adverse events, lost to follow up, and protocol violation.

Efficacy Results

The primary efficacy endpoint of treatment failure cumulative pregnancy rate at 1 year was 0.0%: positive pregnancy test results were reported for 0 of 2045 ITT efficacy subjects in the Combined MPA-SC group and 0 of 268 ITT efficacy subjects in the study 267BMD MPA-IM group. Except for 1 subject in the study 267 MPA-SC group with an inconclusive test result at week 6 (with negative results reported for subsequent tests), all reported pregnancy test results were negative. The Pearl Index, the number of pregnancies per 100 woman-years, was also 0.0. Confidence intervals were not calculated for this index because no pregnancies were reported.

The results of the Phase 3 contraception studies show that MPA-SC is an effective contraceptive in a relevant target population of sexually active women aged 18 through 49 years, including a substantial number of the most fertile population subgroup (aged ≤35 years) who completed 1 year of treatment. No pregnancies due to treatment failure were reported during a combined total of 23,205 woman-cycles of exposure to MPA-SC or during 19,588 woman-cycles of exposure over periods when subjects were at risk for pregnancy (ie, when months during which barrier contraception was used and months without intercourse were excluded). Efficacy was demonstrated in subjects of various racial groups, although relatively few nonwhite subjects were included in the Phase 3 studies. MPA-SC showed equal efficacy regardless of age, BMI, or concomitant use of CYP3A4 inducers.

Endometriosis

There has been extensive clinical experience with the use of medroxyprogesterone acetate in the effective treatment of endometriosis, however there are no pivotal clinical trials with DEPO-PROVERA intramuscular formulation.

DETAILED PHARMACOLOGY

Medroxyprogesterone acetate (MPA) induces response in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected intramuscularly as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrus cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity, and in dogs, increases serum growth hormone levels.

Clinical Pharmacology (MPA)

Medroxyprogesterone acetate has prolonged progestational effects when administered by intramuscular injection. MPA suppresses the secretion of pituitary gonadotropins which, in turn, prevents follicular maturation, producing long-term anovulation in the reproductive-aged woman.

Clinical studies have not shown signs and symptoms of a hypoestrogenic state in women using MPA as a contraceptive. This finding is supported by laboratory measurements showing that circulating estrogen levels in medroxyprogesterone acetate-treated women are similar to those in the early follicular phase of the menstrual cycle. Cyclic patterns of estrogen levels reappear as MPA serum levels decline.

MPA suppresses the Leydig cell function in the male (i.e., suppresses endogenous testosterone production).

A single dose of 50 mg of parenteral MPA has the equivalent effect of 20 mg of parenteral progesterone given daily for 10 days in producing an optimal secretory change in an estrogen-primed endometrium. This steroid also produces typical progestational changes in the cervical mucus (inhibits ferning), increases the viscosity of cervical mucus thereby increasing the difficulty of sperm penetration of the cervical mucus, and increases the intermediate cell found in the maturation index of the vaginal epithelium.

It has been suggested that long-term use of MPA may indirectly decrease high density lipoprotein cholesterol (HDL-C) by decreasing the production of natural estrogen. The purported lowering of mean HDL-C levels in a group of 23 women receiving MPA for 1 year or more was attributed to the drug's suppression of estrogen production. It has been shown, however, that the natural circulating estrogen is not depressed below that of the early follicular phase concentrations after injection of MPA. Women who used MPA for contraception for 4.4 to 10.6 years had no additional suppression of estrogen beyond that observed following the first injection. Another study has shown that long-term use of MPA causes a moderate decrease in triglycerides, HDL cholesterol, HDL cholesterol/total cholesterol ratio and apolipoprotein A1. Total cholesterol, LDL cholesterol and apolipoprotein B were unaffected.

TOXICOLOGY

Chronic Toxicity

Rat, Mouse:
In 18-month studies, mice given two, 100 or 200 mg/kg (3X, 150X or 300X the human dose) did not show treatment-related neoplasia; even the massive doses produced only minimal toxicity. Rats given two, 100 or 200 mg/kg in 24-month carcinogenicity studies did not show serious adverse effects.

Beagle Dog:
Two 7-year toxicity studies in Beagle dogs were conducted using MPA doses ranging from 1X to 25X the human contraceptive dose. MPA (and progesterone) caused anestrus, obesity, increased production of growth hormone, acromegaly, impaired carbohydrate metabolism, multiple endocrinopathy, glomerulopathy, and marked stimulation of the mammary gland resulting in hyperplasia and neoplasia. These tumours were not new histologic types. Progestogen treatment appeared to potentiate the growth of the same types of tumours that would be expected in control dogs, usually the complex or "mixed" type. Mammary carcinomas were found in MPA-treated dogs in both studies and in progesterone-treated dogs in the second study.

The Committee on Safety of Medicines (United Kingdom) and three international panels of experts have reviewed the evidence and concluded that the Beagle bitch is not an appropriate model for mammary carcinogenicity testing of progesterone derivatives such as DEPO-PROVERA (medroxyprogesterone acetate).

Because of differences between the Beagle bitch and the human female in the sensitivity to and the metabolism of progestogens, positive carcinogenicity studies in the Beagle bitch can no longer be considered as indicative of significant hazard to women.

Rhesus Monkey:
In a 10-year toxicology study of MPA in Rhesus monkeys, MPA was administered at 1X, 10X, and 50X the human contraceptive dose. Mammary nodules diagnosed as focal nodular hyperplasia of the mammary gland were found in 3 of the 7 survivors in the 10X group. The lesions showed no signs of malignancy. Because these lesions were both non-progressive and non-invasive and because many lesions of this type are known to appear and then regress, it was concluded that the occurrence of this non-malignant mammary lesion in three MPA-treated monkeys poses no potential threat of breast cancer to women using DEPO-PROVERA as a contraceptive.

Lesions diagnosed as endometrial carcinoma were found in 2 of the 12 survivors in the 50X group. These 2 were replacements - 1 was treated for 111 months and the other for 125 months of the 130-month study (based on 28-day months). The lesions were remarkably similar in cell morphology to epithelial plaques which occur in monkeys but not in humans. It is possible that MPA provided a uterine environment that allowed proliferation of an epithelial cell type present in the endometrium of the Rhesus monkey and other non-human primates. Under the influence of progesterone, this epithelial cell type responds to implantation by proliferating and forming an epithelial plaque. The cells comprising this plaque are readily distinguished from normal epithelial cells of the endometrium. Under progesterone or progestogen influence, this epithelial cell type also proliferates and forms a plaque in response to experimentally induced endometrial trauma. Results of electron microscopic studies indicated that the neoplasms were malignant and were epithelial and not mesenchymal in origin, and thus of a type not stimulated by progestogens in women. It has been concluded that, regardless of the cause of these lesions, their occurrence does not signify that DEPO-PROVERA is carcinogenic in women using it as a contraceptive.

Mutagenicity
In 3 different mutagenicity tests, MPA showed no mutagenic properties. MPA was not mutagenic in the Salmonella/Microsome Test (Ames test), it did not induce single-strand breaks in DNA in a DNA damage/alkaline elution assay, and in the micronucleus test MPA at 100X the human contraceptive dose did not induce micronuclei (i.e., it was not clastogenic and did not cause abnormal distribution of chromosomal material).

Reproduction and Teratology
Studies have not demonstrated any impairment of fertility in first or second generation studies. In rats, MPA may have some effect on genital systems, but standard teratologic techniques have shown no effects on nongenital systems. MPA produced cleft palates in rabbits, attributed to that particular species' sensitivity to the drug's glucocorticoid activity.

Local Tolerance
A single dose of 104 mg MPA in 0.65 mL of the subcutaneous formulation of MPA was administered to 12 female rabbits. Four rabbits were sacrificed on days 7, 28, and 91 following dosing and the injection sites examined. Erythema and/or edema were observed at 2 sites during the course of the study. Material consistent with the dosing formulation was evident at all 12 injection sites and was associated with a modest localized inflammatory response. Results showed that the formulation was well tolerated. Test material was inadvertently administered intradermally in 2 rabbits. Intradermal injections were less well tolerated with slight degeneration of adjacent connective tissue and slight focal myositis in the cutaneous muscle.

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PART III: CONSUMER INFORMATION

DEPO-PROVERA
DEPO-PROVERA-SC
Medroxyprogesterone acetate
Sterile Aqueous Suspension 50 mg/mL, 104 mg/0.65 mL and 150 mg/mL

This leaflet is Part III of a three-part "Product Monograph" published when DEPO-PROVERA and DEPO-PROVERA-SC was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DEPO-PROVERA and DEPO-PROVERA-SC. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

DEPO-PROVERA is used for:
- Conception control (to prevent pregnancy)
- Treatment of endometriosis

DEPO-PROVERA-SC is used for:
- Conception control (to prevent pregnancy)

DEPO-PROVERA and DEPO-PROVERA-SC should be used as a birth control method only if other treatments have been considered to be unsuitable or unacceptable and should be used for the shortest period of time possible. It should be taken into consideration that the return to fertility following treatment with DEPO-PROVERA / DEPO-PROVERA-SC may be delayed (see Warnings and Precautions, Return of Fertility).

DEPO-PROVERA should be used in endometrial treatment only if other treatments have been considered to be unsuitable or unacceptable and should be used for the shortest period of time possible.

DEPO-PROVERA-SC has not been studied in women under 18 years of age.

What it does:
DEPO-PROVERA and DEPO-PROVERA-SC contains medroxyprogesterone acetate, a substance similar to (but not the same as) the natural hormone progesterone that is produced by ovaries during the second half of the menstrual cycle.

Conception control (to prevent pregnancy)
- Prevent the ripening of the egg in the ovaries. When there is no ripe egg to be fertilized by the sperm, pregnancy cannot occur,
- Change the lining of the uterus (the endometrium) so that it does not easily receive a fertilized egg,
- Cause thickening of the mucus in the cervix, making it more difficult for the sperm to enter the uterus.

Treatment of endometriosis (DEPO-PROVERA only)
The lining of the uterus (womb) is called the endometrium. Part of the endometrium is shed during the menstrual period. In endometriosis, endometrium-like tissue is found outside the uterus, such as around the uterus, ovaries, intestines and other organs in the pelvis. As with normal endometrial tissue, this tissue can be shed during your period. Some women with endometriosis have symptoms such as painful periods, pelvic pain, pain during intercourse and painful bowel movements.

Endometriosis is a disorder that is dependent on the hormone estrogen. It is thought that DEPO-PROVERA works as a treatment for endometriosis by reducing certain hormone levels in the body, including estrogen levels, and by helping to shrink the endometrium-like tissue.

How effective is DEPO-PROVERA?
Contraception: DEPO-PROVERA is more than 99.7 percent effective for conception control. DEPO-PROVERA-SC is as effective as DEPO-PROVERA.

DEPO-PROVERA and DEPO-PROVERA-SC are more effective than IUDs, condoms (sometimes called rubber sheaths or prophylactics), diaphragms, or other contraceptive methods as shown in Table 1.

Other ways to prevent pregnancy
Other methods of contraception are available to you, including sterilization, and IUDs. How well other methods of contraception work depends in part on how reliably they are used. Faithful users may achieve pregnancy rates in the lower ranges, others may expect pregnancy rates more in the middle of the ranges of those shown in Table 1.

Table 1 shows the reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant during the first year of use.

Table 1 - DEPO-PROVERA Sterile Aqueous Suspension Reported Pregnancies per 100 Women per Year

Method		Lowest expected	Typical
DEPO-PROVERA		**0.3**	**0.3**
Female sterilization		0.2	0.4
Male sterilization		0.1	0.15
Oral Contraceptives (the pill)		0.1- 0.5	3
IUD	Copper T 380A	0.8	3
Condom		2	12
Diaphragm		6	18
Sponge	women who have not had any children	6	18
	women who have had children	9	28

Cap	6	18
Withdrawal	4	18
Periodic abstinence	1-9	20
Spermicides	3	21
Chance (no birth control)	85	85

When it should not be used:
You should not use DEPO-PROVERA or DEPO-PROVERA-SC if you have or have had any of the following conditions:
• you are pregnant or suspect you may be pregnant
• unusual vaginal or urinary tract bleeding without a known reason
• known or suspected cancer of the breast, cancer of reproductive organs or progestin-dependent cancer
• breast lumps or breast abnormalities without a known reason
• blood clots in the legs, lungs, eyes or elsewhere, or thrombophlebitis (inflammation of the veins)
• stroke, heart attack, or coronary artery disease (e.g. Angina pectoris)
• severe high blood pressure
• known abnormalities of the blood clotting system that increase your risk for developing blood clots
• very high blood cholesterol or triglyceride levels
• heavy smoking (>15 cigarettes per day) and over age 35
• diabetes with complications
• loss of vision due to blood vessel disease of the eye
• migraine headache
• jaundice (yellowing of the eyes or skin), liver disease or liver tumour
• allergy (hypersensitivity) to medroxyprogesterone acetate or to any of the ingredients in DEPO-PROVERA or DEPO-PROVERA-SC (see **What the medicinal ingredient is** and **What the nonmedicinal ingredients are**).

DEPO-PROVERA or DEPO-PROVERA-SC should not be used before menarche (the onset of menstrual periods).

If you wish to become pregnant in the near future, DEPO-PROVERA or DEPO-PROVERA-SC may not be an appropriate treatment for you. You should discuss alternative treatments with your doctor. **(See The Risks of Using DEPO-PROVERA, Return of Fertility.)**

What the medicinal ingredient is:
Medroxyprogesterone acetate

What the nonmedicinal ingredients are:
DEPO-PROVERA:
Polyethylene glycol 3350, methylparaben, polysorbate 80, propylparaben, sodium chloride and water for injection. When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

DEPO-PROVERA-SC:
methylparaben, propylparaben, sodium chloride, polyethylene glycol, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injection. When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

What dosage forms it comes in:
DEPO-PROVERA (medroxyprogesterone acetate) is supplied in 2 strengths.

50 mg/mL	5 mL vials	Single use only
150 mg/mL	1 mL vials	1 x 1 mL vials; 5 x 1 mL vials, 25 x 1 mL vials

DEPO-PROVERA-SC (medroxyprogesterone acetate) is supplied in 1 strength.

104 mg/ 0.65 mL	0.65 mL pre-filled glass syringe	Single use only

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS
Use of DEPO-PROVERA or DEPO-PROVERA-SC may cause you to lose bone mineral density. The longer you use DEPO-PROVERA or DEPO-PROVERA-SC, the more bone mineral density you may lose. Your bone mineral density may not return completely once you stop using DEPO-PROVERA or DEPO-PROVERA-SC. This is of particular concern when DEPO-PROVERA or DEPO-PROVERA-SC is used in adolescence (teenager years) when you should instead be building bone mineral density. Loss of bone mineral density can cause osteoporosis and increase the risk that your bones might break, especially after menopause (the end of menstrual periods).

DEPO-PROVERA or DEPO-PROVERA-SC should be used as indicated **only** if other treatments have been considered to be unsuitable or unacceptable and should be used for the shortest period of time possible.

The risks and benefits of treatment should be carefully reevaluated on a regular basis in all users of this drug.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. It is advised that you do not smoke.

DEPO-PROVERA or DEPO-PROVERA-SC **does not protect** you against sexually transmitted infections (STIs), including HIV/AIDS. It is advisable to use latex or polyurethane condoms for this purpose.

BEFORE you use DEPO-PROVERA or DEPO-PROVERA-SC talk to your doctor or pharmacist if:

You or any immediate family member has ever had any of the following:

- Breast cancer or family history of breast cancer, abnormal breast exam or x-ray (mammogram)
- Diabetes or family history of diabetes
- Seizures, convulsions, epilepsy
- Migraine (headaches)
- Asthma
- Problems with heart, heart attack
- Stroke, blood clots (coagulation disorder)
- Problems with kidneys
- High blood pressure
- Mental depression or family history of depression
- Scanty or irregular menstrual periods
- Smoke

Tell your doctor if you are scheduled for any laboratory tests or surgery.

DEPO-PROVERA or DEPO-PROVERA-SC should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. You should talk regularly with your doctor about whether you still need treatment with DEPO-PROVERA or DEPO-PROVERA-SC. You should only use DEPO-PROVERA if other methods of birth control or endometrial treatments are not right for you.

Because DEPO-PROVERA and DEPO-PROVERA-SC are a long-acting method of contraception, it takes some time after the last injection for its effect to wear off. This varies from woman to woman. Most women, however, must wait from six to eight months after the last injection to start ovulating, have regular periods, and be able to become pregnant (see **THE RISKS OF USING DEPO-PROVERA - Return of Fertility**).

THE RISKS OF USING DEPO-PROVERA

1. <u>Bone Mineral Changes/Osteoporosis</u>

Use of DEPO-PROVERA or DEPO-PROVERA-SC may cause you to lose bone mineral density. This can cause weak bones (osteoporosis) that can increase the risk that your bones might break, especially after menopause (the end of menstrual periods). The longer you use DEPO-PROVERA or DEPO-PROVERA-SC, the more bone mineral density you may lose. Your bone mineral density may not return completely once you stop using DEPO-PROVERA or DEPO-PROVERA-SC.

The following are also risk factors for low bone mineral density:
- bone disease;
- anorexia nervosa (an eating disorder);
- a strong family history of osteoporosis;
- use of certain medications (e.g. steroids or anti-seizure medications);
- drinking a lot of alcohol;
- smoking.

DEPO-PROVERA or DEPO-PROVERA-SC should be used as indicated **only** if other treatments have been considered to be unsuitable or unacceptable and should be used for the shortest period of time possible. The risks and benefits of treatment should be carefully reevaluated on a regular basis in all users of this drug. If you use DEPO-PROVERA or DEPO-PROVERA-SC, your doctor may ask you to have a bone test, especially if you have other risk factors for weak bones. You should talk to your doctor about how to reduce the risk of low bone mineral density, and how much calcium and vitamin D you should take.

In one study, higher fracture rate observed among DEPO-PROVERA users was principally a result of risk factors other than exposure to DEPO-PROVERA.

2. <u>Formation of Tumours</u>

A long-term examination of women using DEPO-PROVERA or DEPO-PROVERA-SC shows no overall increased risk of ovarian, liver, or cervical cancer. The same examination showed a prolonged, protective effect of reducing the risk of endometrial cancer (cancer of the lining of the uterus) in the population of users.

Women who had ever used DEPO-PROVERA or DEPO-PROVERA-SC showed no increased risk of breast cancer. And overall, there was no increase in risk of breast cancer with increasing duration of use of DEPO-PROVERA or DEPO-PROVERA-SC. However, in a certain set of women, those who first took the drug within the previous 4 years and who were under 35 years of age showed a slight increase of breast cancer associated with use of DEPO-PROVERA or DEPO-PROVERA-SC.

Regular breast examination by a health practitioner and regular breast self-examination are recommended for all women. You should review technique for breast self-examination with your health practitioner.

3. <u>Use in Pregnancy</u>

Do not use DEPO-PROVERA or DEPO-PROVERA-SC if you are pregnant, or think that you may be pregnant. It will not prevent the pregnancy from continuing, but may interfere with the normal development of your baby.

To reduce the risk of using DEPO-PROVERA or DEPO-PROVERA-SC while you are pregnant, get your injection: **only** within the first five days of the beginning of your normal (menstrual) period, or **only** within the first five days after giving birth if you are NOT breast-feeding.

4. <u>Use While Breast-Feeding</u>

Before using DEPO-PROVERA or DEPO-PROVERA-SC while breast-feeding, talk with your doctor. DEPO-PROVERA or DEPO-PROVERA-SC should not affect the amount or quality of your milk. Children whose mothers used DEPO-PROVERA while breast-feeding for about 6 months, showed no harmful effects up to 14-16 years of age. There is no further information on these children beyond 16 years old.

A very small amount of the medicine in DEPO-PROVERA or DEPO-PROVERA-SC is transferred to the milk of nursing mothers. It is recommended that DEPO-PROVERA or DEPO-PROVERA-SC not be used by women who are breast feeding until at least 6 weeks after delivery.

If you are breast feeding, you should discuss the use of DEPO-PROVERA or DEPO-PROVERA-SC with your doctor so that he/she can help you decide what is best in your situation.

5. Thromboembolism (blood clots)

There have been rare cases of heart attack, stroke and blood clots in the legs and lungs in women using DEPO-PROVERA or DEPO-PROVERA-SC. It is important for you to recognize the following symptoms and to call your doctor immediately if you:

- Have sharp chest pain, cough blood, or suddenly have trouble breathing;
- Have a sudden severe headache with vomiting, blindness or trouble talking, weakness, or numbness in an arm or leg, or get dizzy or faint;
- Have swelling or severe pain in your leg.

6. Return of Fertility

DEPO-PROVERA or DEPO-PROVERA-SC will not make you infertile. Because DEPO-PROVERA and DEPO-PROVERA-SC are long-acting methods of contraception, it takes some time after the last injection for its effect to wear off. This varies from woman to woman. Most women, however, must wait from six to eight months after the last injection to start ovulating, have regular periods, and be able to become pregnant.

If you stop using DEPO-PROVERA or DEPO-PROVERA-SC and you do NOT want to become pregnant, start using another method of contraception 3 months after your last injection of DEPO-PROVERA or DEPO-PROVERA-SC.

If you want to become pregnant, tell your doctor. Fifty-four percent of women who wish to become pregnant do so within six months after their last injection of DEPO-PROVERA. Seventy-six percent of all women become pregnant within one year, and 92% became pregnant within two years. The average time to pregnancy is 9 months after the last injection.

Table 2 shows the percent of women that become pregnant after stopping the use of DEPO-PROVERA, oral contraceptives, and IUDs.

Table 2 - DEPO-PROVERA Sterile Aqueous Suspension. The percent of women that become pregnant after stopping the use of DEPO-PROVERA, oral contraceptives ("the pill"), and intrauterine devices (IUDs)

Months since stopping contraception	DEPO-PROVERA Users	"The Pill" Users	IUD Users
6	54%	75%	60%
12	76%	85%	76%
24	92%	95%	93%

The effect of DEPO-PROVERA-SC can last for a long time after you stop getting injections. In DEPO-PROVERA users, time to pregnancy might be a little longer compared to non-DEPO-PROVERA users.

In rare cases, it can take two years or longer for ovulation and regular periods to return, and for you to be able to become pregnant. This delay in return of fertility (after stopping DEPO-PROVERA injections) is not related to how long DEPO-PROVERA has been used. In very rare cases, women have not become pregnant after stopping injections of DEPO-PROVERA. The reason is not known. There are many reasons why women are unable to become pregnant, including increased age and the start of menopause. In the general population, 7 out of every 100 women are unable to get pregnant.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking, or begin taking, any other medicines, even medicines you buy without a prescription. Some medicines may interfere with each other in your body.

Drugs that may interact with DEPO-PROVERA or DEPO-PROVERA-SC include aminoglutethimide and rifampin.

PROPER USE OF THIS MEDICATION

Usual Dose

Conception control (contraception):

Injections Every Three Months

DEPO-PROVERA is injected into muscle - for example, into the fleshy part of the hip (buttocks) or upper arm.

For DEPO-PROVERA to prevent you from getting pregnant, you must get an injection of 150 mg every three months (up to 13 weeks).

DEPO-PROVERA-SC is injected just under the skin on your thigh or belly.

For DEPO-PROVERA-SC to prevent you from getting pregnant, you must get an injection of 104 mg every three months (up to 14 weeks).

The First Injection

If your bleeding pattern is unusual, have a pregnancy test before you receive your first injection.

Do not use DEPO-PROVERA or DEPO-PROVERA-SC if you are pregnant, or think that you may be pregnant. It will not prevent the pregnancy from continuing, but may interfere with the normal development of your baby. For this reason, get your first injection: **only** within the first 5 days from the beginning of your (menstrual) period, or **only** within the first 5 days after giving birth if you are NOT breast-feeding. Before using DEPO-PROVERA or DEPO-PROVERA-SC while breast-feeding, discuss with your doctor. When this procedure is followed, DEPO-PROVERA or DEPO-PROVERA-SC will be effective from the day of injection.

If DEPO-PROVERA or DEPO-PROVERA-SC is given after the first 5 days of the beginning of your (menstrual) period, it may not prevent you from getting pregnant for the first 3 to 4 weeks after the injection. Use another non-hormonal contraceptive method (e.g. condom, diaphragm, sponge, cervical cap, abstinence) during these 3 to 4 weeks.

Repeat Injections
See your doctor a week or two early if you know that it will be difficult to get your next injection three months after the last one. This contraceptive method does require you to plan ahead. If scheduling injections every three months would be difficult, then DEPO-PROVERA or DEPO-PROVERA-SC is probably not the best contraceptive method for you.

Duration of Use
You should discuss with your doctor the length of time that you should use DEPO-PROVERA or DEPO-PROVERA-SC.

Steps After Childbirth, Miscarriage or Therapeutic Abortion
If you plan to use DEPO-PROVERA or DEPO-PROVERA-SC following childbirth, get your injection during the first five days after giving birth if you are NOT breast-feeding. If you choose to breast-feed, discuss with your doctor the possibility of getting pregnant, other possible contraceptives, and when you may start using DEPO-PROVERA or DEPO-PROVERA-SC. (See **WARNINGS AND PRECAUTIONS, Use While Breast-Feeding)**

After miscarriage or therapeutic abortion, talk to your doctor about when you may start using DEPO-PROVERA or DEPO-PROVERA-SC.

Missed Dose:
If You Miss Your Injection of DEPO-PROVERA
You can get your injection up to 13 weeks, or as early as 10 weeks, after your last injection. If you have not had your injection by the 13th week, you should have a pregnancy test done before any further injections.

If You Miss Your Injection of DEPO-PROVERA-SC

You can get your injection up to 14 weeks, or as early as 12 weeks, after your last injection. If you have not had your injection by the 14th week, you should have a pregnancy test done before any further injections.

Endometriosis:
The recommended dose is 50 mg once weekly or 100 mg injected into the muscle every 2 weeks for at least 6 months.

Overdose
Overdose may cause lack of or irregular menstrual bleeding.

In case of drug overdose, contact your physician and/or your local Poison Control Centre, or hospital emergency department immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some women have side effects from this medicine. Remember, medicines affect different people in different ways. Just because side effects have occurred in other women, this does not mean you will get them. The side effect that occurs most often is change in menstrual patterns.

Osteoporosis and Fracture
There have been cases of osteoporosis and fracture (broken bones) among DEPO-PROVERA users.

Changes In Menstrual Patterns (during treatment)
DEPO-PROVERA or DEPO-PROVERA-SC slowly and continuously releases a hormone into your body for about three months. Because of this, you are not likely to have regular periods. For the first three to six months, most women have irregular, unpredictable or even continuous bleeding. The bleeding may be as heavy as a typical period or it may be lighter. This unpredictable bleeding pattern may be inconvenient, but it is normal due to the change DEPO-PROVERA or DEPO-PROVERA-SC causes in the lining of your uterus. The lining no longer thickens each month and therefore, does not need to be lost as menstrual flow.

As you continue to use DEPO-PROVERA or DEPO-PROVERA-SC, bleeding generally decreases until most women no longer have monthly periods by the end of the first year of use. The lack of bleeding is NOT a sign of pregnancy. However, if you think you may be pregnant, contact your doctor as soon as possible. Consider using another method of contraception if you think that irregular or complete lack of menstrual periods would upset you.

After you stop using DEPO-PROVERA or DEPO-PROVERA-SC, the uterine lining will start to thicken again. Periods will start again as soon as the effects of DEPO-PROVERA or DEPO-PROVERA-SC completely wear off. The time this takes varies from woman to woman.

Very heavy bleeding that persists for several days is NOT a normal effect of DEPO-PROVERA or DEPO-PROVERA-SC. If this happens, call your doctor immediately.

Weight Gain

Some women gain weight due to an increased appetite while using DEPO-PROVERA or DEPO-PROVERA-SC. If you notice a large increase in your weight in a short period of time that is not easily explained, tell your doctor. The weight gain observed with DEPO-PROVERA-SC was lower than in DEPO-PROVERA users.

Mental Depression

Women who have a history of depression may find that DEPO-PROVERA will worsen this condition. If this happens to you, or if you become depressed, tell your doctor.

Other Side Effects

Just as some women notice bodily changes before their period, you may notice some of the same changes after an injection of DEPO-PROVERA. Although reported less often than changes in bleeding patterns, the following side effects were reported in studies of 3,905 women receiving DEPO-PROVERA every three months. Tell your doctor right away if any of the following continue, bother you, or are not easily explained:

• irregular menstrual bleeding	• swelling of the hands or feet
• amenorrhea	• backache
• headache	• depression
• nervousness	• insomnia
• abdominal cramps	• acne
• dizziness	• pelvic pain
• weakness or fatigue	• no hair growth or excessive hair loss
• decreased sexual desire	• rash
• leg cramps	• hot flashes
• nausea	• joint pain
• vaginal discharge or irritation	• bloating
• breast swelling and tenderness	

The injection itself may cause slight pain and a slight lump may appear under the skin. The lump will usually disappear in a few days.

Like any medication, DEPO-PROVERA-SC may cause some side effects. Other very common side effects with DEPO-PROVERA-SC are headache, backache, fatigue, decreased sexual desire, depression, acne, and skin reactions at the injection site.

Skin reactions may cause lumps, skin dimpling, or pain which are usually mild and usually don't last long. Scarring is unusual, but may happen. If there is swelling or your skin gets hot, has pus or looks bruised one or more days after your shot, call your healthcare provider.

Other problems were reported by very few of the women in the clinical trials, but some of these could be serious. These include: convulsions, jaundice, urinary tract infections, allergic reactions, fainting, paralysis, osteoporosis, lack of return to fertility, deep vein thrombosis, pulmonary embolus, breast cancer, or cervical cancer. If these or any other problems occur during your use of DEPO-PROVERA, discuss them with your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/possible side effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain, nausea or vomiting		√	
	Persistent sad mood			√
	Unusual swelling of the extremities		√	
	Skin reaction at the injection site	√		
Uncommon	Bone fractures (broken bones)			√
	Breast lump		√	
	Convulsions or seizure			√
	Crushing chest pain or heaviness			√
	Hives, rash, mouth or facial swelling			√
	Pain or swelling in the leg			√
	Sharp pain in the chest, coughing blood, or sudden shortness of breath			√
	Sudden partial or complete loss of vision or double vision			√
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm			√

	or leg			
	Unexpected vaginal or urinary tract bleeding		√	
	Yellowing of the skin or eyes (jaundice)			√

This is not a complete list of side effects. If you have any unexpected effects after taking DEPO-PROVERA or DEPO-PROVERA-SC, contact your doctor or pharmacist.

HOW TO STORE IT

DEPO-PROVERA
Protect from freezing. Store upright at controlled room temperature 15° to 30° C. Shake well before using. Keep out of reach of children.

DEPO-PROVERA-SC
Protect from freezing. Store at controlled room temperature 15° to 25°C. Shake well before using. Keep out of reach of children. Do not bend.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: **Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.**

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, may be obtained at: http://www.pfizer.ca or by contacting the sponsor, Pfizer Canada Inc. at: 1-800-463-6001.

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