PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]TARO-MEDROXYPROGESTERONE INJECTION

medroxyprogesterone acetate injectable suspension

Suspension, 150 mg/mL, Intramuscular

Taro Std.

Progestogen

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RECENT MAJOR LABEL CHANGES

Not applicable	

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TARO-MEDROXYPROGESTERONE INJECTION (medroxyprogesterone acetate injectable suspension) is indicated for:

- conception control (prevention of pregnancy)
- treatment of endometriosis

TARO-MEDROXYPROGESTERONE INJECTION 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 TARO-MEDROXYPROGESTERONE INJECTION may be delayed (see **7 WARNINGS AND PRECAUTIONS**).

Since loss of bone mineral density (BMD) may occur in females of child-bearing potential who use TARO-MEDROXYPROGESTERONE INJECTION long-term (see **7 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 medroxyprogesterone acetate, all patients should have adequate calcium and vitamin D intake. Cessation of smoking and regular weight bearing exercise should be discussed with all patients.

1.1 Pediatrics

- Pediatrics (12-18 years): In adolescents, use of TARO-MEDROXYPROGESTERONE INJECTION is only indicated when other contraceptive methods are considered unsuitable or unacceptable, due to unknown long-term effects of bone loss associated with medroxyprogesterone acetate during the critical period of bone accretion (see **7 WARNINGS AND PRECAUTIONS**).

1.2 Geriatrics

- Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

TARO-MEDROXYPROGESTERONE INJECTION (medroxyprogesterone acetate injectable suspension) 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 **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

TARO-MEDROXYPROGESTERONE INJECTION should not be used before menarche.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- The use of medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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.

- TARO-MEDROXYPROGESTERONE INJECTION 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 (see **7 WARNINGS AND PRECAUTIONS**).

  Women considering using TARO-MEDROXYPROGESTERONE INJECTION should be advised about the concerns that TARO-MEDROXYPROGESTERONE INJECTION may increase risk of HIV acquisition, about the uncertainty over whether there is a causal relationship, and about how to minimize their risk of acquiring HIV.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Conception Control: The recommended dose for contraception is 150 mg of TARO-MEDROXYPROGESTERONE INJECTION every 3 months, administered by deep 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 breastfeeding. If the woman has chosen to breastfeed, discuss the risks of pregnancy and possible risks of TARO-MEDROXYPROGESTERONE INJECTION to determine the most appropriate course of action for the individual woman (see **7 WARNINGS AND PRECAUTIONS**).

If administered within the first 5 days after the onset of a normal menstrual period, TARO-MEDROXYPROGESTERONE INJECTION is effective from the day of injection. When TARO-MEDROXYPROGESTERONE INJECTION 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, TARO-MEDROXYPROGESTERONE INJECTION 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 TARO-MEDROXYPROGESTERONE INJECTION within 7 days after taking their last active pill).

Endometriosis: The recommended dose of TARO-MEDROXYPROGESTERONE INJECTION 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 **7 WARNINGS AND PRECAUTIONS**).

Use in Children: TARO-MEDROXYPROGESTERONE INJECTION should not be used before menarche

(see **2 CONTRAINDICATIONS**). See **7 WARNINGS AND PRECAUTIONS**, Loss of Bone Mineral Density

for available data for adolescent females (12-18 years).

4.4 Administration

TARO-MEDROXYPROGESTERONE INJECTION is intended for **INTRAMUSCULAR ADMINISTRATION ONLY**.

Immediately before use, the sterile aqueous suspension should be vigorously shaken to assure that the dose being administered represents a uniform suspension.

4.5 Missed Dose

If an injection is not given within 13 weeks of the last TARO-MEDROXYPROGESTERONE INJECTION dose, a pregnancy test should be done before any further treatment with TARO-MEDROXYPROGESTERONE INJECTION.

5 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 medroxyprogesterone acetate (500 mg daily or more) have been associated with corticoid-like activity and with Cushingoid symptoms (e.g. moon face and blood pressure elevation). There is no known therapy for overdosage.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular	Suspension 150 mg/mL	Methylparaben, polyethylene glycol 3350, polysorbate 80, propylparaben, sodium chloride, hydrochloric acid and/or sodium hydroxide (for pH adjustment), and water for injection

Each mL of TARO-MEDROXYPROGESTERONE INJECTION contains:

Ingredients (mg)	150 mg/mL (vial)
Medroxyprogesterone acetate	150
Polyethylene Glycol 3350	28.9
Polysorbate 80	2.41
Sodium Chloride	8.68
Methylparaben	1.37
Propylparaben	0.15
Water for injection, Sodium Hydroxide and Hydrochloric acid	q.s.

*Amount of excipients presented as mg/mL of suspension

TARO-MEDROXYPROGESTERONE INJECTION is supplied in 1 strength (150 mg/mL) as 1 x 1 mL vials.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

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.**

Counseling when used for conception control:

It is very important that adequate explanations of the long-term nature of TARO-MEDROXYPROGESTERONE INJECTION 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 TARO-MEDROXYPROGESTERONE INJECTION for conception control.

Sexually Transmitted Infections:

Some epidemiological evidence on hormonal contraceptive methods and the risk of HIV acquisition suggests a possible increase in risk of HIV acquisition in women who use the depot medroxyprogesterone acetate or medroxyprogesterone acetate injectable suspension. However, since the evidence comes from observational studies, which are vulnerable to certain methodological biases, it remains unclear if the association is definitively causal. If the association between medroxyprogesterone acetate and HIV acquisition risk is causal, data suggest a likely increase in risk of hazards ratio 1.5 or less.

Women considering using TARO-MEDROXYPROGESTERONE INJECTION should be advised about the concerns that TARO-MEDROXYPROGESTERONE INJECTION may increase risk of HIV acquisition, about the uncertainty over whether there is a causal relationship, and about how to minimize their risk of acquiring HIV. Women should be counseled that TARO-MEDROXYPROGESTERONE INJECTION does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS). Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV. The benefits of contraceptive options and their risks must be evaluated individually for each woman.

Carcinogenesis and Mutagenesis

Long-term, case-controlled surveillance of users of medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 TARO-MEDROXYPROGESTERONE INJECTION, 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 TARO-MEDROXYPROGESTERONE INJECTION 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate use in this population. Before prescribing TARO-MEDROXYPROGESTERONE INJECTION, 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 medroxyprogesterone acetate (see **8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions**). Generally, it is not clear if the risk of cardiovascular events is different for users of medroxyprogesterone acetate than for non-users.

Hypertension

There have been reports of cerebro/cardiovascular adverse events in medroxyprogesterone acetate 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 **2 CONTRAINDICATIONS**).

Endocrine and Metabolism

Loss of Bone Mineral Density

Use of medroxyprogesterone acetate reduces serum estrogen levels and is associated with a statistically 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate injection is discontinued and ovarian estrogen production increases.

In adolescence, following medroxyprogesterone acetate use for more than 2 years, subjects did not recover to their baseline BMD level at the femoral neck and total hip even up to 60 months.

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.

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

Long term use

BMD should be monitored in women using TARO-MEDROXYPROGESTERONE INJECTION 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 TARO-MEDROXYPROGESTERONE INJECTION should be reconsidered.

Use of TARO-MEDROXYPROGESTERONE INJECTION should be considered a risk factor for osteoporosis. The use of TARO-MEDROXYPROGESTERONE INJECTION 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 and BMD Recovery Post-treatment in Adult Women

In a controlled, open-label, non-randomized clinical study (medroxyprogesterone acetate n=248, placebo n=360), adult women using medroxyprogesterone acetate (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. There were no significant changes in BMD in the control women over the same period of time. Table 2 shows the extent of recovery of BMD for women who received one or more medroxyprogesterone acetate injections during Years 1 through 5.

Table 2 – 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	
	Medroxy-progesterone acetate **	Control***	Medroxy-progesterone acetate **	Control***	Medroxy-progesterone acetate **	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.*

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

*** *The control group consisted of women who did not use medroxyprogesterone acetate prior to the indicated time point.*

† *Women who took one or more doses of medroxyprogesterone acetate, 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 medroxyprogesterone acetate (150 mg IM), there was partial 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)

The impact of medroxyprogesterone acetate (150 mg) use for up to 240 weeks (4.6 years) was evaluated in an open- label non-randomized clinical study in 389 adolescent females (12-18 years). Use of medroxyprogesterone acetate was associated with a significant decline from baseline in BMD.

Partway through the trial, drug administration was stopped (at 120 weeks). The mean number of injections per medroxyprogesterone acetate user was 9.3. The decline in BMD at total hip and femoral neck was greater with longer duration of use (see Table 3). The mean decrease in BMD at 240 weeks was more pronounced at total hip (-6.4%) and femoral neck (-5.4%) compared to lumbar spine (-2.1%).

In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynecologic age, race, BMD and other factors that influence the rate of acquisition of bone mineral density.

Table 3 – Mean Percent Change from Baseline in BMD in Adolescents Receiving ≥4 Injections per 60-week Period, by Skeletal Site and Cohort

Duration of Treatment	Medroxyprogesterone acetate CI (150 mg IM)		Unmatched, Untreated Cohort	
	N	Mean % Change	N	Mean % Change
Total Hip BMD				
Week 60 (1.2 years)	113	-2.75	166	1.22
Week 120 (2.3 years)	73	-5.40	109	2.19
Week 240 (4.6 years)	28	-6.40	84	1.71
Femoral Neck BMD				
Week 60	113	-2.96	166	1.75
Week 120	73	-5.30	108	2.83
Week 240	28	-5.40	84	1.94
Lumbar Spine BMD				
Week 60	114	-2.47	167	3.39
Week 120	73	-2.74	109	5.28
Week 240	27	-2.11	84	6.40

BMD Recovery Post-Treatment in Adolescents

Longer duration of treatment and smoking were associated with less recovery of BMD following the last injection of medroxyprogesterone acetate. Table 4 shows the extent of recovery of BMD up to 60 months post- treatment for adolescent women who received medroxyprogesterone acetate for two years or less compared to more than two years. Post-treatment follow-up showed that, in women treated for more than two years, only lumbar spine BMD recovered to baseline levels after treatment was discontinued. Subjects treated with medroxyprogesterone acetate for more than two years did not recover to their baseline BMD level at femoral neck and total hip even up to 60 months post-treatment. Adolescent women in the untreated cohort gained BMD throughout the trial period (data not shown).

Table 4 – Extent of BMD Recovery (Months Post-Treatment) in Adolescents by Years Medroxyprogesterone acetate Use (2 Years or Less vs. More than 2 Years)

Duration of Treatment	2 years or less		More than 2 years	
	N	Mean % Change from baseline	N	Mean % Change from baseline
Total Hip BMD				
End of Treatment	49	-1.5%	49	-6.2%
12 M post-treatment	33	-1.4%	24	-4.6%
24 M post-treatment	18	0.3%	17	-3.6%
36 M post-treatment	12	2.1%	11	-4.6%
48 M post-treatment	10	1.3%	9	-2.5%
60 M post-treatment	3	0.2%	2	-1.0%
Femoral Neck BMD				
End of Treatment	49	-1.6%	49	-5.8%
12 M post-treatment	33	-1.4%	24	-4.3%
24 M post-treatment	18	0.5%	17	-3.8%
36 M post-treatment	12	1.2%	11	-3.8%
48 M post-treatment	10	2.0%	9	-1.7%
60 M post-treatment	3	1.0%	2	-1.9%
Lumbar Spine BMD				
End of Treatment	49	-0.9%	49	-3.5%
12 M post-treatment	33	0.4%	23	-1.1%
24 M post-treatment	18	2.6%	17	1.9%
36 M post-treatment	12	2.4%	11	0.6%
48 M post-treatment	10	6.5%	9	3.5%
60 M post-treatment	3	6.2%	2	5.7%

Relationship of Fracture Incidence to Use of medroxyprogesterone acetate *(150 mg IM) or Non-Use by Women of Reproductive Age*

A retrospective cohort study to assess the association between medroxyprogesterone acetate injection and the incidence of bone fractures was conducted in 312,395 female contraceptive users in the UK. The incidence rates of fracture were compared between medroxyprogesterone acetate users and contraceptive users who had no recorded use of medroxyprogesterone acetate. 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). It is not known if this is due to medroxyprogesterone acetate use or to other related lifestyle factors that have a bearing on fracture rate.

In the study, when cumulative exposure to medroxyprogesterone acetate was calculated, the fracture rate in users who received fewer than 8 injections was higher than that in women who received 8 or more injections. However, it is not clear that cumulative exposure, which may include periods of intermittent use separated by periods of non-use, is a useful measure of risk, as compared to exposure measures based on continuous use.

There were very few fractures at skeletal sites known to be related to low BMD in the study and the incidence of these fractures was not found to be higher in medroxyprogesterone acetate users compared to non-users. Importantly, this study could not determine whether use of medroxyprogesterone acetate has an effect on fracture rate later in life.

In post-marketing experience, there have been cases of osteoporosis including osteoporotic fractures reported in patients taking medroxyprogesterone acetate. Patient age ranged from 16 years to 48 years (see **8 ADVERSE REACTIONS, 8.5 Post-Market Adverse 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 medroxyprogesterone acetate. The mechanisms of this decrease are obscure. For this reason, diabetic women should be carefully observed while receiving TARO-MEDROXYPROGESTERONE INJECTION.

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 TARO-MEDROXYPROGESTERONE INJECTION (see **8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, Weight Gain Experience**). 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**.** 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 medroxyprogesterone acetate users actually lose weight during treatment.

Genitourinary

Irregular Menstrual Patterns

Disruption of menstrual patterns is common following the administration of medroxyprogesterone acetate. 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 medroxyprogesterone acetate, 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 medroxyprogesterone acetate.

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

Hematologic

There have been post-market reports of arterial and venous thromboembolism (VTE) in women using medroxyprogesterone acetate (see **8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions**). Generally, it is not clear if the risk of arterial and venous thromboembolism is different for users of medroxyprogesterone acetate 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 medroxyprogesterone acetate. If an anaphylactic reaction occurs, appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

Monitoring and Laboratory Tests

Before TARO-MEDROXYPROGESTERONE INJECTION 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 TARO-MEDROXYPROGESTERONE INJECTION 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 TARO-MEDROXYPROGESTERONE INJECTION should be reconsidered. (See **7 WARNINGS AND PRECAUTIONS**).

Neurologic

CNS Disorders and Convulsions

There have been few reported cases of convulsions in patients who were treated with medroxyprogesterone acetate. Association with medroxyprogesterone acetate 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 **2 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

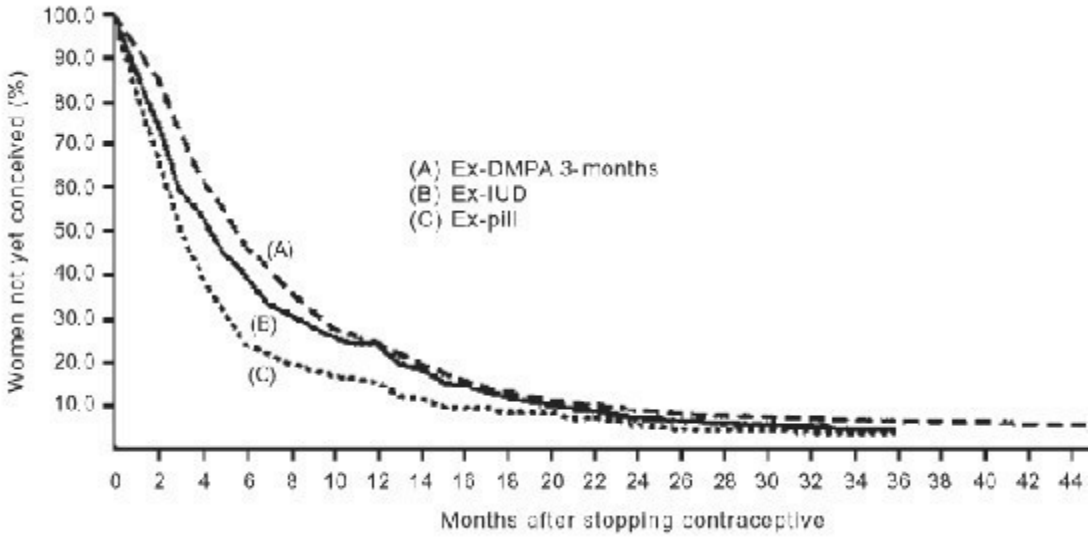
Women who have a history of mental depression should be carefully observed and this drug discontinued if serious depression re-occurs. Some women may complain of premenstrual like depression while on TARO-MEDROXYPROGESTERONE INJECTION therapy.

Reproductive Health: Female and Male Potential

- **Fertility**

  There is no evidence that medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate in order to become pregnant



In some cases, women have not become pregnant after stopping injections of medroxyprogesterone acetate. It is not known whether medroxyprogesterone acetate 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%.

- **Ectopic Pregnancy**

  Physicians should investigate the possibility of an ectopic pregnancy among women using medroxyprogesterone acetate who complain of severe abdominal pain.

7.1 Special Populations

7.1.1 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 breastfeeding (see **4 DOSAGE AND ADMINISTRATION**).

Infants from unexpected pregnancies that occurred 1 to 2 months after injection of medroxyprogesterone acetate 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 medroxyprogesterone acetate, 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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.

7.1.2 Breast-feeding

Detectable amounts of progestogen have been identified in the milk of mothers receiving medroxyprogesterone acetate. Two studies have indicated that the maximum amount of medroxyprogesterone acetate which might be ingested by a breastfeeding infant whose mother is receiving medroxyprogesterone acetate 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 medroxyprogesterone acetate was started 1-4 days, 7 days or within 6 weeks postpartum.

In nursing mothers treated with medroxyprogesterone acetate, milk composition, quality and amount are not adversely affected.

To date, no adverse effects have been observed in children whose mothers were using medroxyprogesterone acetate while lactating. A study of children exposed to medroxyprogesterone acetate 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 TARO-MEDROXYPROGESTERONE INJECTION not be administered until 6 weeks postpartum in women who are breastfeeding 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 TARO-MEDROXYPROGESTERONE INJECTION 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 medroxyprogesterone acetate while lactating.

7.1.3 Pediatrics

TARO-MEDROXYPROGESTERONE INJECTION should not be used before menarche (see **2 CONTRAINDICATIONS**). In adolescents, use of TARO-MEDROXYPROGESTERONE INJECTION is only indicated when other contraceptive methods are considered unsuitable or unacceptable, due to unknown long-term effects of bone loss associated with medroxyprogesterone acetate during the critical period of bone accretion.

7.1.4 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

7.1.5 Other

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions have been associated with the use of medroxyprogesterone acetate:

(A) *Irregular Menstrual Patterns*
The most common adverse reactions associated with the use of medroxyprogesterone acetate 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In clinical studies of 3,905 women receiving medroxyprogesterone acetate 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 5 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 6 contains the number of side effects reported by month and the number of side effect reports per 100 patients "exposed" by month.

Table 5 – MEDROXYPROGESTERONE ACETATE 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
Vomiting	16	12	0.31

Symptom	No. of Times Reported	No. of Women Reporting	Percent of Women (3,905)
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 6, 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 6 –MEDROXYPROGESTERONE ACETATE EVERY 90 DAYS SIDE EFFECTS – 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

Month	# Pts Entering/Month	# Reports	# Reports/100 Patients
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
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 medroxyprogesterone acetate 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 medroxyprogesterone acetate. 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

Injection Period	Months	Percent of Days with Bleeding and/or Spotting
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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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	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 medroxyprogesterone acetate 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
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

SYSTEM ORGAN CLASS	EVENT
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%) 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

8.5 Post-Market Adverse Reactions

In post-marketing experience, there have been cases of osteoporosis including osteoporotic fractures reported in patients taking medroxyprogesterone acetate. 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 medroxyprogesterone acetate.

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), injections site pain/tenderness, injection site persistent atrophy/indentation/dimpling/scar, injection site nodule/lump, malaise, sudden infant death syndrome (exposure-in utero)

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

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: abnormal genitalia, anencephaly, antepartum hemorrhage, blighted ovum, cleft palate, congenital adenomatoid malformation, congenital diaphragmatic hernia, congenital heart defects, congenital megacolon, ear malformation NOS, ectopic pregnancy, esophageal atresia, fetal hydrops, hydrocephalus, hypospadias, intrauterine growth retardation, limb deformity, microcephaly, missed abortion, polydactyly, polyhydramnios, prematurity, single umbilical artery, skull malformation, spina bifida, spontaneous abortion, stillbirth, Talipes, tracheoesophageal fistula

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, lipodystrophy acquired, porphyria aggravated

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Medroxyprogesterone acetate is metabolized in-vitro primarily by hydroxylation via the CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on medroxyprogesterone acetate 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.

9.4 Drug-Drug Interactions

Aminoglutethimide: Aminoglutethimide administered concomitantly with TARO-MEDROXYPROGESTERONE INJECTION (medroxyprogesterone acetate) may significantly depress the serum concentration of medroxyprogesterone acetate. Users of TARO-MEDROXYPROGESTERONE INJECTION 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Certain endocrine and possibly liver function tests may be affected by treatment with TARO-MEDROXYPROGESTERONE INJECTION. Therefore, if such tests are abnormal in a woman taking TARO-MEDROXYPROGESTERONE INJECTION, 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 TARO-MEDROXYPROGESTERONE INJECTION:

(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: TARO-MEDROXYPROGESTERONE INJECTION does not interfere with the assay of human chorionic gonadotropin (HCG) either chemically or pharmacologically).

10 CLINICAL PHARMACOLOGY

10.2 Pharmacodynamics

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. TARO-MEDROXYPROGESTERONE INJECTION does not contain estrogen.

For conception control, medroxyprogesterone acetate inhibits 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 medroxyprogesterone acetate include the transformation and maintenance of an endometrium hostile to implantation, and thickening of cervical mucus making sperm penetration of the cervix more difficult.

Medroxyprogesterone acetate 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 mechanism of action of medroxyprogesterone acetate 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.

10.3 Pharmacokinetics

Table 7 - Summary of medroxyprogesterone acetate suspension for injection's Pharmacokinetic Parameters in adult women population

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

* not available

Absorption

Following intramuscular administration, medroxyprogesterone acetate 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 medroxyprogesterone acetate in the circulation is between 4 and 20 days. Following a single 150 mg IM dose of medroxyprogesterone acetate injectable suspension, medroxyprogesterone acetate 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 medroxyprogesterone acetate 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.

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.

Medroxyprogesterone acetate binding occurs primarily to serum albumin; no binding of medroxyprogesterone acetate occurs with sex hormone-binding globulin (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.

Elimination

The terminal half-life of medroxyprogesterone acetate 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.

Special Populations and Conditions

- **Hepatic Insufficiency**

  The effect of hepatic disease on the pharmacokinetics of medroxyprogesterone acetate is unknown. However, medroxyprogesterone acetate is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolized in patients with severe liver insufficiency, (see **2 CONTRAINDICATIONS**).

- **Renal Insufficiency**

  The effect of renal disease on the pharmacokinetics of medroxyprogesterone acetate is unknown.

11 STORAGE, STABILITY AND DISPOSAL

Protect from freezing. Unopened vials may be stored between 20°C to 25°C, excursions permitted between 15°C to 30°C. Shake well before using. Keep out of reach and sight of children. Store the vials upright.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

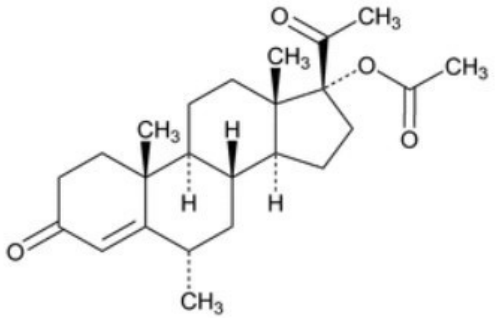
Drug Substance

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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Conception control

The contraceptive efficacy, safety and acceptability of 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 medroxyprogesterone acetate 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					
MEDROXYPROGESTERONE ACETATE 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
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.

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 medroxyprogesterone acetate intramuscular formulation.

14.2 Study Results

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

MEDROXYPROGESTERONE ACETATE
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		
MEDROXYPROGESTERONE ACETATE 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
Medroxyprogesterone acetate 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.

MEDROXYPROGESTERONE ACETATE Sterile Aqueous Suspension Reported Pregnancies per 100 Women per Year			
Method		**Lowest expected**	**Typical**
MEDROXYPROGESTERONE ACETATE		**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

14.3 Comparative Bioavailability Studies

A blinded, randomized, two-treatment, single-period, single dose (1 mL x 150 mg/mL deep intramuscular injection), parallel group comparative bioavailability study of TARO-MEDROXYPROGESTERONE INJECTION injectable suspension, 150 mg/mL (Taro Pharmaceuticals Inc.) and DEPO-PROVERA® injectable suspension, 150 mg/mL (Pfizer Canada Inc.), was conducted in healthy, non-smoking adult female subjects under fasting conditions. Blood samples for pharmacokinetic analysis were collected for up to 151 days post-dose. Comparative bioavailability data from 134 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Medroxyprogesterone Acetate (1 mL x 150 mg/mL) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	3066 3206.16 (24.65)[a]	3400 3456.83 (23.07)[b]	90.2	83.7 – 97.2
AUC_I (ng·h/mL)	3475 3583.22 (19.79)[c]	3679 3733.93 (17.84)[d]	94.5	89.2 – 101.2
$AUC_{0\text{-}90d}$ (ng·h/mL)	2524 2694.22 (31.72)[e]	2866 2934.00 (27.19)[f]	88.1	80.9 – 95.9
C_{max} (pg/mL)	2278 2547.72 (49.57)[e]	2508 2709.95 (48.14)[f]	90.9	80.9 – 102.0
T_{max}[3] (h)	143.38 (1.00 – 3239.08)	192.83 (24.00 – 2665.83)		
$T_{½}$[4] (h)	750.18 (62.75)	686.33 (73.15)		

[1] TARO-MEDROXYPROGESTERONE INJECTION (medroxyprogesterone acetate) injectable suspension, 150 mg/mL (Taro Pharmaceuticals Inc.)

[2] DEPO-PROVERA® (medroxyprogesterone acetate) injectable suspension, 150 mg/mL (Pfizer Canada Inc.)

[3] Expressed as the median (range) only

[4] Expressed as the arithmetic mean (CV %) only

[a] N=68, [b] N=63, [c] N=62, [d] N=59, [e] N=69, [f] N=65

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Chronic Toxicology:

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 medroxyprogesterone acetate (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 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 medroxyprogesterone acetate (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 medroxyprogesterone acetate 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 medroxyprogesterone acetate is carcinogenic in women using it as a contraceptive.

Mutagenicity:

In 3 different mutagenicity tests, medroxyprogesterone acetate (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).

Reproductive and Developmental Toxicology:

Studies have not demonstrated any impairment of fertility in first or second generation studies. In rats, medroxyprogesterone acetate (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.

17 SUPPORTING PRODUCT MONOGRAPHS

[Pr]DEPO-PROVERA® (medroxyprogesterone acetate injectable suspension, 150 mg / mL), Submission Control 262875 Product Monograph, Pfizer Canada ULC, SEP 07, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTARO-MEDROXYPROGESTERONE INJECTION

Medroxyprogesterone acetate injectable suspension

Read this carefully before you are given **TARO-MEDROXYPROGESTERONE INJECTION** and each time you receive an injection. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TARO-MEDROXYPROGESTERONE INJECTION**.

Serious Warnings and Precautions

- Low Bone Density (osteoporosis): TARO-MEDROXYPROGESTERONE INJECTION may cause your bones to become less dense. This can lead to osteoporosis or broken bones. It is worse the longer you use the drug. The effect on your bones may not be reversed by stopping the drug. This is of concern because adolescence and young adulthood are times to build bone density for later in life.
- Only use TARO-MEDROXYPROGESTERONE INJECTION if you and your healthcare professional decide that no other treatment will work for you.
- Use it for the shortest period of time possible.
- Your risks and benefits should be regularly re-evaluated by you and your healthcare professional.
- You should not smoke. It increases the risk of serious side effects on the heart and blood vessels.
- TARO-MEDROXYPROGESTERONE INJECTION DOES NOT PROTECT against sexually transmitted infections. This includes HIV/AIDS. Use condoms (latex or polyurethane) to reduce the risk.
- Women considering using TARO-MEDROXYPROGESTERONE INJECTION should be advised about the concerns that TARO-MEDROXYPROGESTERONE INJECTION may increase risk of HIV acquisition, about the uncertainty over whether there is a causal relationship, and about how to minimize their risk of acquiring HIV.

What is TARO-MEDROXYPROGESTERONE INJECTION used for?

- birth control to prevent pregnancy
- treatment of endometriosis

How does TARO-MEDROXYPROGESTERONE INJECTION work?

For birth control: TARO-MEDROXYPROGESTERONE INJECTION works in 3 ways to make pregnancy unlikely:

- stops the maturing of the egg in the ovaries
- changes the lining of the uterus
- thickens the mucous in the cervix

TARO-MEDROXYPROGESTERONE INJECTION is more than 99.7 percent effective in preventing pregnancy.

For treatment of endometriosis: TARO-MEDROXYPROGESTERONE INJECTION helps shrink endometrium-like tissue found outside the uterus.

What are the ingredients in TARO-MEDROXYPROGESTERONE INJECTION?

Medicinal ingredients: medroxyprogesterone acetate

Non-medicinal ingredients: Methylparaben, polyethylene glycol, polysorbate, propylparaben, sodium chloride, and water for injection. It may also contain hydrochloric acid, sodium hydroxide or both.

TARO-MEDROXYPROGESTERONE INJECTION comes in the following dosage forms:

Vials of sterile Aqueous Suspension: 150 mg/mL

Do not use TARO-MEDROXYPROGESTERONE INJECTION if:

- You are pregnant or think you might be
- Your menstrual periods have not started
- You have unusual vaginal bleeding without a known reason
- You have blood in your urine
- You have or suspect a cancer. It can be of the breast, uterus or ovaries. It can be a cancer that grows in response to progesterone.
- You have breast lumps or breast abnormalities without a known reason
- You have had blood clots in the legs, lungs, eyes or another part of the body, or inflammation of the veins (thrombophlebitis)
- You have or have had problems with your blood clotting system that increase your risk of developing blood clots (including coagulation disorders)
- You have had a stroke, heart attack, heart disease or coronary artery disease
- You have severe high blood pressure
- You have very high levels of blood cholesterol or triglycerides
- You are a heavy smoker (more than 15 cigarettes per day) and are over age 35
- You have diabetes with complications
- You have had a loss of vision due to blood vessel disease of the eye
- You have or have had migraine headaches with auras such as changes in your vision, sensations, balance, muscle coordination, or speech
- You have yellowing of the eyes or skin (jaundice), liver disease or a liver tumour
- You are allergic to medroxyprogesterone acetate or to any of the ingredients in TARO-MEDROXYPROGESTERONE INJECTION

If you want to get pregnant in the near future, you should discuss other treatments with your healthcare professional. TARO-MEDROXYPROGESTERONE INJECTION may not be the right treatment for you.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive TARO-MEDROXYPROGESTERONE INJECTION. Talk about any health conditions or problems you may have, including if you:

- Have a family history of breast cancer, or an abnormal breast exam or mammogram
- Have diabetes, or a family history of it
- Have seizures, convulsions or epilepsy
- Have migraine headaches
- Have asthma
- Have any heart problems
- Have kidney problems

- Have high blood pressure, or a family history of it

- Have or have had mental depression
- Have menstrual periods that are very light or that occur in an irregular pattern
- Have a history of smoking or are a current smoker
- Have a scheduled lab test or surgery

Other warnings you should know about:

Sexually Transmitted Infections: TARO-MEDROXYPROGESTERONE INJECTION may increase the risk of HIV acquisition. Talk to your healthcare professional about how to minimize the risk of getting HIV.

Low Bone Density (osteoporosis): TARO-MEDROXYPROGESTERONE INJECTION may cause your bones to become less dense. Other risk factors for low bone density are:

- bone disease
- strong family history of osteoporosis
- use of certain steroids or anti-seizure drugs
- drinking a lot of alcohol
- smoking
- low body weight or anorexia nervosa or bulimia (eating disorders)

Talk with your healthcare professional about how:

- to keep your risk as low as possible
- to strengthen your bones

Cancer: Use of this drug has not shown an increased risk of cancer of the liver, breast, ovary, or cervix. There is a decrease risk of cancer of the uterus.

Some women who took TARO-MEDROXYPROGESTERONE INJECTION got breast cancer. This seems to occur if:

-you were under 35 years old when you took the drug.

AND

-you used the drug in the 4 years before being diagnosed with breast cancer.

Talk to your healthcare professional about breast self-examination.

Blood clots: Talk to your healthcare professional if you develop risk factors for blood clots. These include:

- start smoking
- obesity
- recent major surgery (such as hip or knee replacement)
- immobility due to air travel or other reason
- lupus

Pregnancy: You should not use TARO-MEDROXYPROGESTERONE INJECTION if you are pregnant, or think that you may be pregnant. It will not prevent the pregnancy from continuing. It may interfere with the normal development of your baby.

When might you get pregnant after stopping the injections?

If you want to become pregnant, tell your healthcare professional. TARO-MEDROXYPROGESTERONE INJECTION will not make you infertile. It takes time after the last injection for the drug's effect to wear off. Most women wait six to eight months to start ovulating and have regular periods. This must occur before you can get pregnant.

After their last injection, women get pregnant:

- within 6 months, 54%
- within 1 year, 76%
- within 2 years, 92%

It can take more than 2 years for some women to get pregnant. This does not depend on how long the drug was used.

What if you do NOT want to get pregnant after stopping the injections?
You must start using another method of birth control 3 months after your last injection.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TARO-MEDROXYPROGESTERONE INJECTION:

- Aminoglutethimide: a drug used to treat Cushing's syndrome.
- Rifampin: a drug used to treat tuberculosis (TB) and some other infections.

How is TARO-MEDROXYPROGESTERONE INJECTION given to patients:

TARO-MEDROXYPROGESTERONE INJECTION is given as an injection by your healthcare professional. TARO-MEDROXYPROGESTERONE INJECTION is injected deep into the muscles of your buttock or upper arm.

Usual dose:

For birth control:
First injection:

- If your period bleeding pattern is not normal for you, have a pregnancy test first.
- Get your first injection within 5 days of starting your period. If this is followed, TARO-MEDROXYPROGESTERONE INJECTION will start working on the day of the injection.
- If the injection is given after the first 5 days of your period, it may not start to protect you from pregnancy for another 3-4 weeks. During these 3-4 weeks you MUST use another non-hormonal birth control method.

Ongoing Injections:
Get an injection every 3 months. If you can't see your healthcare professional right at 3 months, you can go a week or two early.

After a miscarriage or abortion: Talk with your healthcare professional about when you may start using TARO-MEDROXYPROGESTERONE INJECTION.

After having a baby, if you are:

- **NOT breastfeeding or NOT planning to breastfeed:**
  Get your first injection during the 5 days after having your baby. It will start working as soon as you have the injection.
- **Breastfeeding or planning to breastfeed:**
  It is recommended to wait at least 6 weeks after having your baby before you get an injection. A very small amount of drug will go into your milk. This drug should not affect the amount or quality of your milk. Talk with your healthcare professional to determine the risk to the baby or of getting pregnant.

  Talk with your healthcare professional about the chance that you may get pregnant during this time. You and your healthcare professional can decide what other birth controls to use, and when you can start the drug.

For endometriosis:
Treatment should last for at least 6 months with either:

- One 50 mg injection every week
- One 100 mg injection every 2 weeks

Overdose:

If you think you, or a person you are caring for, have been given too much TARO-MEDROXYPROGESTERONE INJECTION, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have not had an injection within 13 weeks of your last injection, you should have a pregnancy test before getting any further injections. This is in case you became pregnant in the meantime.

What are possible side effects from using TARO-MEDROXYPROGESTERONE INJECTION?

These are not all the possible side effects you may have when taking TARO-MEDROXYPROGESTERONE INJECTION. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- tiredness, problems sleeping
- leg cramps, joint pain, backache
- pain in your pelvic area, lower sex drive, hot flashes, bloating
- acne
- skin reaction, pus collection, pain or tenderness at the injection site
- lump, dent, dimple, scar or change in colour at injection site (may be persistent)
- nervousness, dizziness
- no hair growth or excessive hair growth

You may gain weight because your appetite has increased. If you notice this over a short period of time, tell your healthcare professional to make a plan about what to do.

Change in your periods:

- more or less often
- lighter or heavier

For the first 3 to 6 months after the first injection, bleeding:

- can come and go
- can't be predicted
- can last much longer than usual

Over the next few months, bleeding:

- usually becomes lighter

After about a year, your periods:

- may stop completely

TARO-MEDROXYPROGESTERONE INJECTION can cause low bone density. Your healthcare professional will decide when to perform bone density tests and interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Abdominal pain, nausea or vomiting		√	
Headache or a migraine that gets worse		√	
Depression: sad mood that doesn't go away. If you have a history of depression, this drug may make your depression worse.			√
Very heavy bleeding that lasts for several days		√	
Edema: swelling of the arms and legs		√	
UNCOMMON			
Broken bones			√
Osteoporosis: weak bones, increased risk that your bones might break especially as you get older than 50		√	
Breast lumps, swelling and tenderness		√	
Convulsions or seizures			√
Pain or heaviness in the chest			√
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Blood clot in the leg (deep vein thrombosis): leg swelling or pain			√
Blood clot in the lung: sharp chest pain, coughing up blood, or sudden shortness of breath			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Blood clot in the eye: **s**udden loss of all or part of your vision or double vision			√
Stroke or blood clot in the brain: a sudden severe headache, vomiting, dizziness, fainting, problems with your vision or speech, weakness, or numbness in the face, arm or leg			√
Cancer of the cervix: Unexpected bleeding from the vagina		√	
Urinary tract Infection: blood in urine. Pain when you go pee.		√	
Jaundice: Yellowing of the skin or eyes			√
Paralysis: it is hard or you are unable to move a part of your body			√
UNKNOWN FREQUENCY			
Heart Attack: gradual chest pain, tightness pressure or squeezing. Pain in the arm, jaw or back. Trouble breathing, anxiety, and sweating			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

TARO-MEDROXYPROGESTERONE INJECTION will be stored by your healthcare professional. If not, this is what to do:

- Store between 20°C to 25°C
- Make sure the drug does not freeze
- Store vials upright
- Keep out of reach and sight of children

If you want more information about TARO-MEDROXYPROGESTERONE INJECTION:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website at www.taro.ca, or by calling 1-800-268-1975.

This leaflet was prepared by Taro Pharmaceuticals Inc.

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