Medroxyprogesterone Acetate Injection I.P.

SAYANA® PRESS

Suspension for Injection in Pre-Filled Injection System

1. GENERIC NAME

Medroxyprogesterone Acetate Injection I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Medroxyprogesterone Acetate single-dose container with 104 mg medroxyprogesterone acetate I.P. (MPA) in 0.65 ml, suspension for injection.

List of Excipients

Methylparaben
Propylparaben
Sodium Chloride
Polyethylene Glycol 3350
Polysorbate 80
Monobasic Sodium Phosphate
Disodium Phosphate
Dodecahydrate Methionine
Povidone K 17 PF
Sodium Hydroxide or Hydrochloric Acid#
Water for Injection
to adjust the pH.

3. DOSAGE FORM AND STRENGTH

Dosage Form: Suspension for injection

Strength: 104 mg/0.65 mL

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Medroxyprogesterone Acetate injectable SC suspensions is indicated for:
Long term female contraception.
Management of endometriosis-associated pain.

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4.2 Posology and Method of Administration

Important Dosage and Administration Instructions

Medroxyprogesterone Acetate is only for subcutaneous administration and may be administered by a healthcare professional or, when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

Use for longer than 2 years is not recommended (unless other birth control methods or medical therapies for endometriosis-associated pain are considered inadequate) due to the impact of long-term Medroxyprogesterone Acetate treatment on bone mineral density (BMD) (see Section 4.4 *Special Warnings and Precautions for Use*).

Prior to the first injection confirm that the patient is not pregnant. For women who are sexually active and who have regular menses, administer the first injection only during the first 5 days of a normal menstrual period. For women who are breast-feeding, administer the first injection during or after the sixth postpartum week.

The recommended dosage of Medroxyprogesterone Acetate is 104 mg given subcutaneously every 12 to 14 weeks. If more than 14 weeks elapse between injections, confirm that the patient is not pregnant before the next injection. Instruct the patient that if they are unable to receive an injection within 12-14 weeks, another contraceptive method should be used until the next Medroxyprogesterone Acetate injection. The dosage does not need to be adjusted for body weight.

Inject the entire contents of the pre-filled single dose injector using strict aseptic technique into the upper anterior thigh or abdomen, rotating the sites with every injection.

Switching from Another Method of Contraception

When switching from another contraceptive method to Medroxyprogesterone Acetate, administer Medroxyprogesterone Acetate in a manner that ensures continuous contraceptive coverage. Follow the respective recommendations when switching from the contraceptive methods listed below:

- Combined hormonal contraceptives: administer the first injection of Medroxyprogesterone Acetate within 7 days after the last day of using the combined hormonal contraceptive method (i.e., within 7 days after taking the last active pill).
- An implant: administer the first injection of Medroxyprogesterone Acetate on the day of implant removal.
- A contraceptive vaginal ring or transdermal system: administer the first injection of Medroxyprogesterone Acetate on the day the patient would have inserted the next ring or applied the next transdermal system.
- An Intrauterine Device (IUD) or Intrauterine System (IUS): administer the first injection of Medroxyprogesterone Acetate on the day of IUD/IUS removal. If the IUD/IUS is not removed on the first day of the patient's menstrual cycle, instruct patients to use a non-hormonal back-up method of birth control for the first 7 days after administration of Medroxyprogesterone Acetate.

- Depot medroxyprogesterone acetate injectable suspension for intramuscular use (DMPA-IM): inject Medroxyprogesterone Acetate 12 to 14 weeks after the last dose of DMPA-IM.

4.3 Contraindications

The use of Medroxyprogesterone Acetate is contraindicated in the following conditions:

- Active thrombophlebitis, or current or history of thromboembolic disorders, or cerebral vascular disease (see Section 4.4 *Special Warnings and Precautions for Use*).
- Known, suspected, or past malignancy of the breast (see Section 4.4 *Special Warnings and Precautions for Use*).
- Significant liver disease (see Section 4.4 *Special Warnings and Precautions for Use*).
- Known hypersensitivity to medroxyprogesterone acetate or any of the ingredients in Medroxyprogesterone Acetate (see Section 4.4 *Special Warnings and Precautions for Use*).
- Undiagnosed vaginal bleeding (see Section 4.4 *Special Warnings and Precautions for Use*).

4.4 Special Warnings and Precautions for Use

Loss of Bone Mineral Density

Use of Medroxyprogesterone Acetate reduces serum estrogen levels and is associated with significant loss of bone mineral density (BMD). This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of Medroxyprogesterone Acetate by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

A study to assess the reversibility of loss of BMD in adolescents was conducted with DMPA-IM. After discontinuing DMPA-IM in these adolescents, mean BMD loss at the total hip and femoral neck did not fully recover by 5 years (60 months) post-treatment in the sub-group of adolescents who were treated for more than 2 years (see Section 6.1 *Animal Toxicology or Pharmacology* **-** Clinical Studies). Similarly, in adults, there was only partial recovery of mean BMD at the total hip, femoral neck, and lumbar spine towards baseline by 2 years post-treatment (see Section 6.1 *Animal Toxicology or Pharmacology* **-** Clinical Studies).

The use of Medroxyprogesterone Acetate is not recommended as a long-term (i.e., longer than 2 years) birth control method or medical therapy for endometriosis-associated pain unless other options are considered inadequate. BMD should be evaluated when a woman needs to continue to use Medroxyprogesterone Acetate long-term. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.

Other birth control methods or therapies for endometriosis-associated pain should be considered in the risk/benefit analysis for the use of Medroxyprogesterone Acetate in women with osteoporosis risk factors. Medroxyprogesterone Acetate can pose an additional risk in patients with risk factors for osteoporosis (e.g., metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids).

Arterial and Venous Thromboembolic Disorders

There have been reports of serious arterial and venous thrombotic events in women treated with DMPA-IM. Women with a history of thromboembolic disorders were not studied in clinical trials of Medroxyprogesterone Acetate. Although no causal relationship between the use of Medroxyprogesterone Acetate and thrombotic events has been clearly established, patients who develop arterial or venous thrombosis while taking Medroxyprogesterone Acetate should discontinue treatment.

Do not re-administer Medroxyprogesterone Acetate pending examination if there is a sudden onset of a suspected vascular ocular event (e.g., partial or complete loss of vision, proptosis, or diplopia) or migraine. Do not re-administer Medroxyprogesterone Acetate if examination reveals papilledema or retinal vascular lesions.

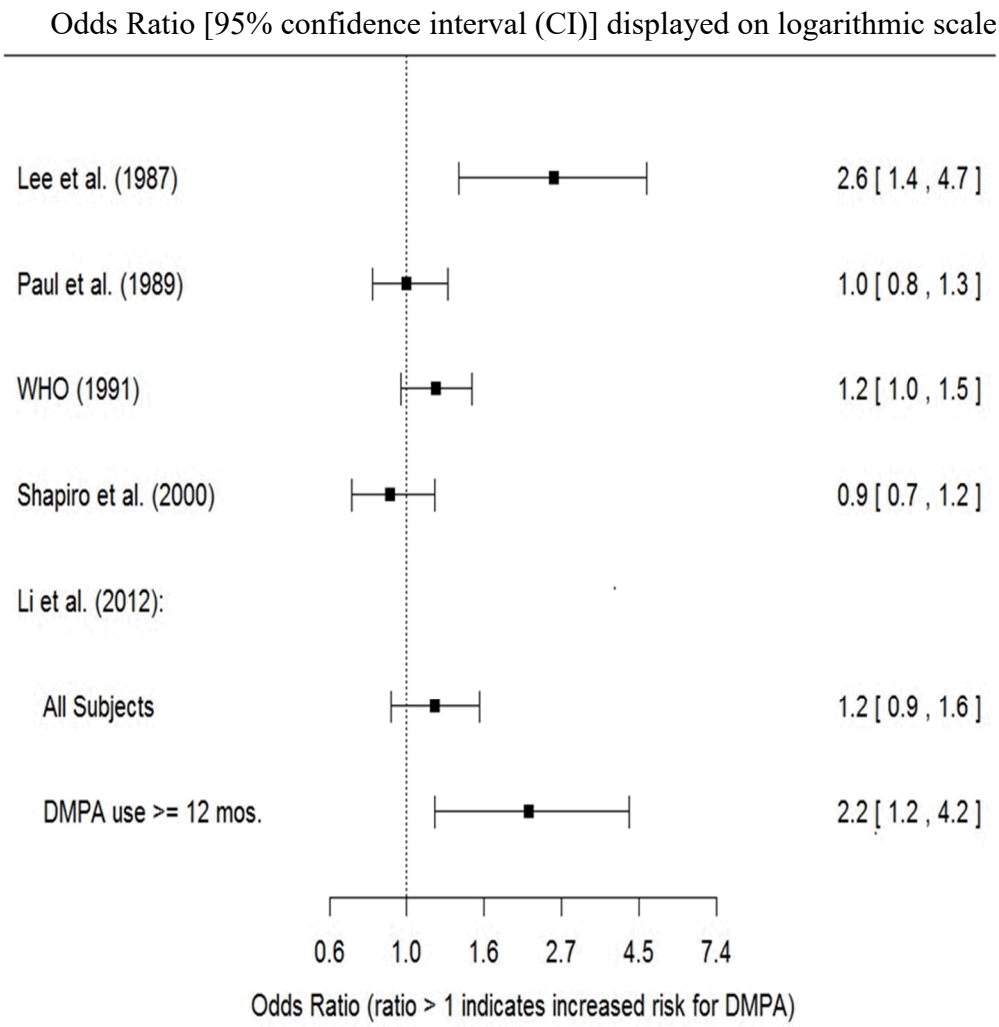
Cancer Risks

Breast Cancer

The use of hormonal contraceptives, including Medroxyprogesterone Acetate, is contraindicated in women who have or have had breast cancer because breast cancer may be sensitive to hormones (see Section 4.3 *Contraindications*). Women who have a family history of breast cancer or a significant risk of breast cancer should be monitored.

The results of five large case-control studies assessing the association between DMPA-IM use and the risk of breast cancer are summarized in Figure M. Three of the studies suggest a slightly increased risk of breast cancer in the overall population of users; these increased risks were statistically significant in one study. One US study evaluated the timing and duration of use and found a statistically significant increased risk of breast cancer in recent DMPA-IM users (defined as last use within the past five years) who used DMPA-IM for 12 months or longer; this is consistent with results of a previous study.

Figure M. Risk Estimates of Breast Cancer in DMPA-IM Users



Odds ratio estimates were adjusted for the following covariates:
Lee et al. (1987): age, parity, and socioeconomic status.
Paul et al. (1989): age, parity, ethnic group, and year of interview.
WHO (1991): age, center, and age at first live birth.
Shapiro et al. (2000): age, ethnic group, socioeconomic status, and any combined estrogen/progestogen oral contraceptive use.
Li et al. (2012): age, year, BMI, duration of OC use, number of full-term pregnancies, family history of breast cancer, and history of screening mammography.

Based on the published SEER-18 2015 incidence rate (age-adjusted to the 2000 US Standard Population) of breast cancer for US women, all races, age 20 to 49 years, a doubling of risk would increase the incidence of breast cancer in women who use DMPA-IM from about 73 to about 146 cases per 100,000 women.

Other Cancers

The relative rate of invasive squamous-cell cervical cancer in women who ever used DMPA-IM 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.

Long-term, case-controlled surveillance of users of DMPA-IM found no overall increased risk of ovarian or liver cancer.

Ectopic Pregnancy

Healthcare professionals should be alert to the possibility of an ectopic pregnancy among women using Medroxyprogesterone Acetate who become pregnant or complain of severe abdominal pain.

Anaphylaxis

Serious anaphylactic reactions have been reported in women using Medroxyprogesterone Acetate. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be administered.

Fluid Retention

Because progestational drugs including Medroxyprogesterone Acetate may cause fluid retention, monitor patients with conditions that might be affected by fluid retention.

Weight Gain

Weight gain is a common occurrence in women using Medroxyprogesterone Acetate. In three large clinical trials using Medroxyprogesterone Acetate, the mean weight gain was 3.5 lb (1.6 kg) in the first year of use. In a small, two-year study comparing Medroxyprogesterone Acetate to DMPA-IM, the mean weight gain observed for women using Medroxyprogesterone Acetate [7.5 lb (3.4 kg)] was similar to the mean weight gain for women using DMPA-IM [7.6 lb (3.5 kg)].

Although there are no data related to weight gain beyond 2 years for Medroxyprogesterone Acetate, the data on DMPA-IM may be relevant. In a clinical study, after five years, 41 women using Depo-Provera CI (150 mg) had a mean weight gain of 11.2 lb (5.1 kg), while 114 women using non-hormonal contraception had a mean weight gain of 6.4 lb (2.9 kg).

Delayed Return of Ovulation or Fertility

Return to ovulation is likely to be delayed after stopping Medroxyprogesterone Acetate, as demonstrated in a study of 15 women who received multiple doses of Medroxyprogesterone Acetate:

- Median time to ovulation was 10 months after the last injection.
- Earliest return to ovulation was 6 months after the last injection.
- 12 women (80%) ovulated within 1 year of the last injection.

However, ovulation has occurred as early as 14 weeks after a single dose of Medroxyprogesterone Acetate; therefore, administer the next Medroxyprogesterone Acetate 12 to 14 weeks after the last injection.

Return to fertility also is likely to be delayed after stopping therapy. Among 28 women using Medroxyprogesterone Acetate for contraception who stopped treatment to become pregnant, 7 women were lost to follow-up. One woman became pregnant within one year of her last injection and another woman became pregnant 443 days after her last injection. The remaining 19 women had not become pregnant; it is not known if these 19 women were still attempting to become pregnant or if they had started a new contraceptive

method.

Depression

Depression (3% of Medroxyprogesterone Acetate-treated patients) and other mood disorders have been reported in clinical trials of Medroxyprogesterone Acetate (see Section 4.*8Undesirable Effects*). Patients with a history of depression or who are on treatment for depression may be at increased risk for depression recurrence or exacerbation and for associated mood disorders while receiving Medroxyprogesterone Acetate. Therefore, patients should be monitored for symptoms of depression and mood changes.

Injection Site Reactions

In five clinical studies of Medroxyprogesterone Acetate involving 2325 women (282 treated for up to 6 months, 1780 treated for up to 1 year, and 263 women treated for up to 2 years), 5% of women reported injection site reactions (such as pain/tenderness, nodule/lump, lipodystrophy, discoloration), and 1% had persistent atrophy/indentation/dimpling (see Section 4.*8 Undesirable Effects*).

These injection site reactions have also been reported in post-marketing experience.

Bleeding Irregularities

Most women using Medroxyprogesterone Acetate experienced changes in menstrual bleeding patterns, such as amenorrhea, irregular unpredictable spotting or bleeding, prolonged spotting or bleeding, or heavy bleeding (see Section 4.8*Undesirable Effects*). Fewer women experienced irregular bleeding and more experienced amenorrhea with longer term use of Medroxyprogesterone Acetate, consistent with expected endometrial thinning effects.

In three contraception trials, 39% of 2053 Medroxyprogesterone Acetate-treated women experienced amenorrhea during Month 6, and 57% experienced amenorrhea during Month 12. In two endometriosis trials using Medroxyprogesterone Acetate, 24% of 289 women experienced amenorrhea during Month 6 (see Section 4.8*Undesirable Effects*).

If abnormal bleeding is persistent or severe, evaluate the patient for underlying pathology or pregnancy.

Risk of Hyperglycemia in Patients with Diabetes

Some patients receiving progestins may exhibit a decrease in glucose tolerance; therefore, patients with diabetes may be at greater risk of hyperglycemia.

Jaundice and Elevated Transaminase

Discontinue Medroxyprogesterone Acetate if jaundice or elevated transaminase levels develop. Medroxyprogesterone Acetate may be resumed after both the jaundice and elevated transaminase levels resolve, and the healthcare professional determines that Medroxyprogesterone Acetate did not cause the abnormalities.

Protection Against Sexually Transmitted Infections

Patients should be counseled that this product does not protect against HIV infection (including AIDS) and other sexually transmitted infections.

4.5 Drugs Interactions

Effect of Other Drugs on Medroxyprogesterone Acetate

Moderate or Strong CYP3A Inducers

Concomitant use with moderate or strong CYP3A inducers may decrease concentrations of medroxyprogesterone acetate which may reduce Medroxyprogesterone Acetate efficacy. This effect is based upon the primary metabolism of medroxyprogesterone acetate by CYP3A and was not confirmed by a clinical study.

Avoid coadministration of Medroxyprogesterone Acetate with moderate or strong CYP3A inducers. Some examples of moderate CYP3A inducers are bosentan, efavirenz, etravirine, and modafinil. Some examples of strong CYP3A inducers are rifampin, carbamazepine, phenytoin, phenobarbital, mitotane, and St. John's wort (the CYP3A4 induction effect of St. John's wort varies widely and is preparation dependent). These examples are a guide and do not represent a comprehensive list of all possible drugs that may fit these categories.

The use of CYP3A inducers may require using a back-up or alternate contraceptive method.

4.6 Use in Special Populations

Pregnancy

There is no use for Medroxyprogesterone Acetate in pregnancy and therefore Medroxyprogesterone Acetate should be discontinued during pregnancy. There appears to be little or no increased risk of birth defects in women who have inadvertently been exposed to medroxyprogesterone acetate injections in early pregnancy. Neonates 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.

Nursing Mothers

Although medroxyprogesterone acetate is detectable in the milk of mothers receiving DMPA-IM, milk composition, quality, and amount do not appear to be adversely affected. Effects on milk production and lactation initiation/duration remain unclear when administered before 6 weeks after delivery. Neonates and infants exposed to medroxyprogesterone acetate from breast milk have been studied for developmental and behavioral effects through puberty, and no adverse effects have been noted.

Pediatric Use

Medroxyprogesterone Acetate is indicated for the prevention of pregnancy and management of endometriosis-associated pain in females of reproductive age. Efficacy is expected to be the same for post-menarchal females under the age of 17 as for users

17 years and older.

Use of Medroxyprogesterone Acetate is associated with significant loss of bone mineral density (BMD). This loss of BMD is of particular concern during adolescence, a critical period of bone accretion. It is unknown if use of Medroxyprogesterone Acetate by female adolescents will reduce peak bone mass and increase the risk for osteoporotic fractures in later life. In a study of adolescent females (12-18 years of age) receiving DMPA-IM for contraception, mean BMD 2 years after starting DMPA-IM decreased 1.9% (spine), 4.3% (total hip), and 4.2% (femoral neck). In those adolescents who used DMPA-IM for more than 2 years, mean BMD at total hip and femoral neck did not return to baseline within 5 years.

Medroxyprogesterone Acetate is not indicated before menarche.

Geriatric Use

Medroxyprogesterone Acetate is not indicated in post-menopausal women.

4.7 Effects on Ability to Drive and Use Machines

No information available.

4.8 Undesirable Effects

The following important adverse reactions are described in more detail in other sections of the prescribing information:

- Loss of bone mineral density (see Section 4.4 *Special Warnings and Precautions for Use*)
- Arterial and venous thromboembolic disorders (see Section 4.4 *Special Warnings and Precautions for Use*)
- Anaphylaxis (see Section 4.4 *Special Warnings and Precautions for Use*)
- Fluid retention (see Section 4.4 *Special Warnings and Precautions for Use*)
- Delayed return of ovulation or fertility (see Section 4.4 *Special Warnings and Precautions for Use*)
- Depression (see Section 4.4 *Special Warnings and Precautions for Use*)
- Injection site reactions (see Section 4.4 *Special Warnings and Precautions for Use*)
- Bleeding irregularities (see Section 4.4 *Special Warnings and Precautions for Use*)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Medroxyprogesterone Acetate in five clinical trials involving 2325 women including 2043 women who received treatment for contraception (1780 treated up to 1 year and 263 treated for up to 2 years) and 282 women for endometriosis for up to 6 months. In these pooled trials, 9% of women discontinued

treatment due to an adverse reaction and the most common reason for discontinuation was dysfunctional uterine bleeding (3%).

Adverse Reactions in the Contraception Adult Studies

Table 1 presents frequently reported adverse reactions (>1%) in the contraception pooled studies. In these studies, the most frequently reported adverse reactions (>5%) were dysfunctional uterine bleeding (e.g., irregular, increased, decreased, or spotting), headache, increased weight, amenorrhea, and injection site reactions (e.g., pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling or lipodystrophy).

The frequency reported is based on the all-causality incidence in the pooled results of the three contraception studies. Closely related "Adverse Reaction" terms were grouped but individual patients reporting two or more grouped events were only counted once.

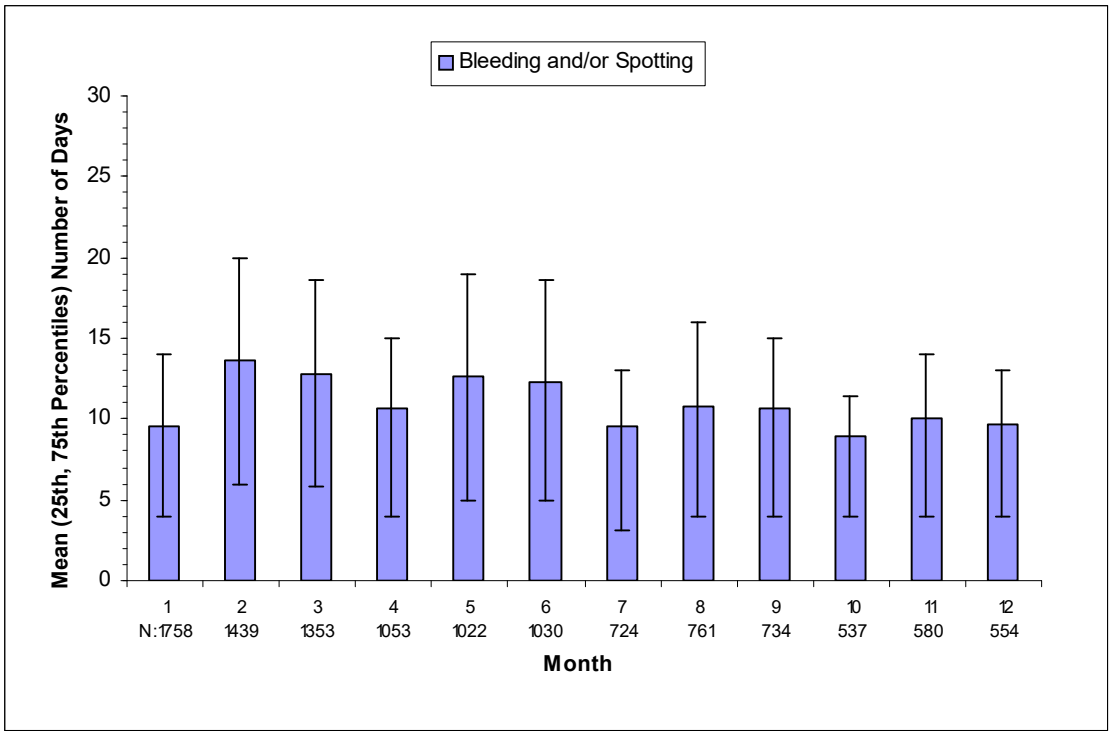
Table 1. Frequently Reported Adverse Reactions in the Contraception Studies (>1%)

Adverse Reaction	Frequency
Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)	18%
Headache	9%
Increased weight (see below)	7%
Amenorrhea	6%
Injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy, discoloration)	6%
Vaginitis, including candidiasis and bacterial	5%
Abdominal pain	4%
Urinary tract infections	4%
Acne	4%
Depression	3%
Decreased libido	3%
Nausea	3%
Back pain	3%
Breast pain/tenderness	2%
Fatigue	2%
Anxiety	1%
Irritability	1%
Dizziness	1%

Dysfunctional Uterine Bleeding

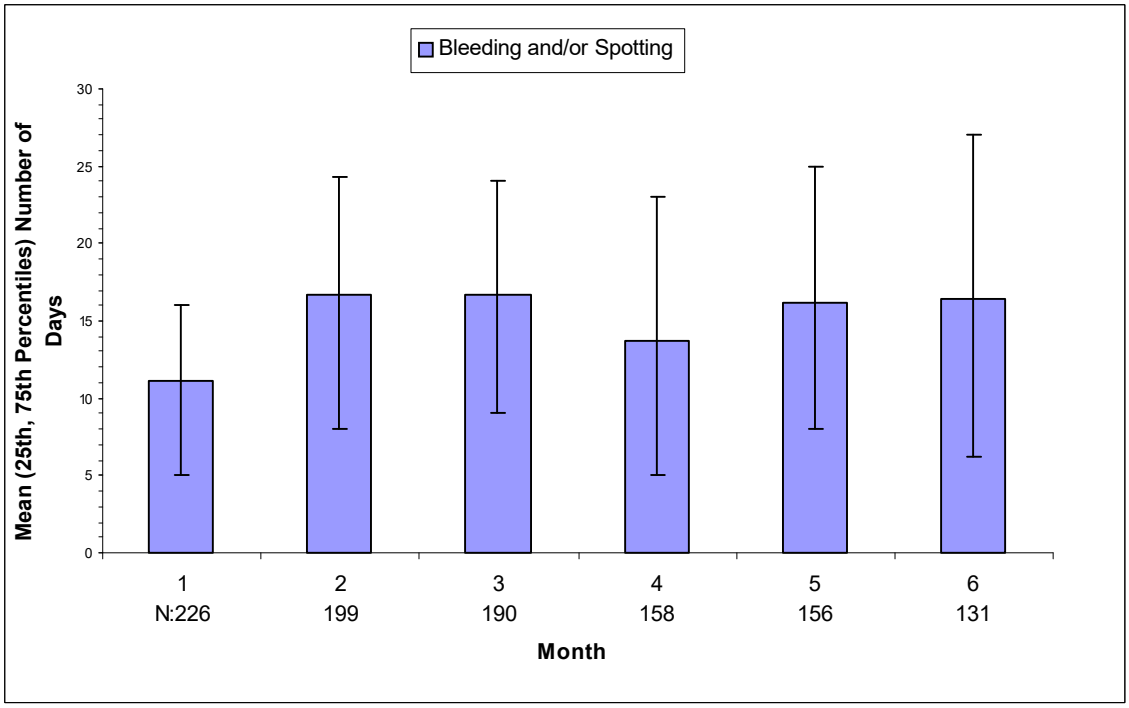
The extent of bleeding and spotting in the three contraception trials is presented in Figure N; data from the endometriosis trials are presented in Figure O (Section 4.4 *Special Warnings and Precautions for Use*).

Figure N. Mean Number of Bleeding or Spotting Days in the Subgroup of Women with Bleeding or Spotting Among Women Treated with Medroxyprogesterone Acetate in Contraception Studies



N=Number of subjects with bleeding or spotting during indicated month.

Figure O. Mean Number of Bleeding or Spotting Days in the Subgroup of Women with Bleeding or Spotting Among Women Treated with Medroxyprogesterone Acetate in Endometriosis Studies



N=Number of subjects with bleeding or spotting during indicated month.

Weight Gain

In three large clinical trials, the mean weight gain in Medroxyprogesterone Acetate treated patients was 3.5 lb (1.6 kg) in the first year of use. Half (50%) of women remained within 4.9 lb (2.2 kg) of their initial body weight; 12% of women lost more than 4.9 lb

(2.2 kg), and 38% of women gained more than 5.1 lb (2.3 kg). In a small, 2-year study comparing Medroxyprogesterone Acetate to DMPA-IM, the mean weight gain observed for women using Medroxyprogesterone Acetate [7.5 lb (3.4 kg)] was similar to the mean weight gain for women using DMPA-IM [7.7 lb (3.5 kg)].

Other Adverse Reactions Observed in Contraception Clinical Trials with Medroxyprogesterone Acetate

Other adverse reactions occurring at an incidence of <1% in women who received Medroxyprogesterone Acetate were as follows:

- Neoplasms benign, malignant and unspecified (including cysts and polyps): breast lump
- Blood and lymphatic system disorders: anemia
- Immune system disorders: drug hypersensitivity
- Metabolism and nutrition disorders: weight decreased, fluid retention
- Nervous system disorders: facial palsy, syncope, paresthesia, somnolence
- Cardiac disorders: tachycardia
- Vascular disorders: hot flushes
- Respiratory, thoracic and mediastinal disorders: asthma, dyspnea
- Gastrointestinal disorders: diarrhea, abdominal distension
- Skin and subcutaneous tissue disorders: urticaria, pruritus, dry skin
- Reproductive system and breast disorders: dysmenorrhea, galactorrhea, dyspareunia
- General disorders and administration site conditions: chest pain

Adverse Reactions in the Endometriosis Adult Studies

The safety profile of Medroxyprogesterone Acetate in endometriosis clinical trials was similar to the safety profile of Medroxyprogesterone Acetate in the contraception studies with the exception of the following adverse reactions which were more frequently reported in patients with endometriosis: abdominal pain, diarrhea, nausea, and back pain.

In endometriosis studies, subjects recorded daily the occurrence and severity of hot flushes. Of the Medroxyprogesterone Acetate users, 29% reported experiencing moderate or severe hot flushes at baseline, 36% at Month 3, and 27% at Month 6. Of the leuprolide users, 33% reported experiencing moderate or severe hot flushes at baseline, 74% at Month 3, and 69% at Month 6.

Adverse Reactions in the Adolescent Contraception Study

Medroxyprogesterone Acetate and DMPA-IM clinical trials reported similar safety profiles in adult study populations (see Table 1 above). Accordingly, a similar safety profile is expected for adolescents receiving Medroxyprogesterone Acetate as for adolescents receiving DMPA-IM.

The safety profile of DMPA-IM for prevention of pregnancy in adolescents was observed to be generally similar to the safety profile of adult women using DMPA-IM for prevention of pregnancy, with the exception of the following adverse reactions which

were reported more frequently by adolescents: abdominal pain, diarrhea, back pain, weight increased, depression, headache, and dysmenorrhea.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of DMPA-IM. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Immune system disorders: anaphylactic reaction, anaphylactoid reaction, angioedema
- Vascular disorders: pulmonary embolism, deep vein thrombosis, thrombophlebitis
- Musculoskeletal and connective tissue disorders: osteoporosis (including osteoporotic fractures)
- Reproductive system and breast disorders: prolonged anovulation, unexpected pregnancy, uterine hyperplasia
- Respiratory, thoracic and mediastinal disorders: hoarseness
- Skin and subcutaneous tissue disorders: increased body odor
- Gastrointestinal disorders: gastrointestinal disturbances
- General disorders and administration site conditions: axillary swelling, chills, thirst

4.9 Overdose

No positive action is required other than cessation of therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Medroxyprogesterone Acetate inhibits the secretion of gonadotropins, which primarily prevents follicular maturation and ovulation and causes thickening of cervical mucus. These actions contribute to its contraceptive effect.

Suppression of serum estradiol concentrations is likely to be responsible for the therapeutic effect on endometriosis-associated pain.

5.2 Pharmacodynamic Properties

The following laboratory tests are expected to be affected by progestins including Medroxyprogesterone Acetate:

- Plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol).
- Gonadotropin levels are decreased.
- Sex-hormone-binding-globulin concentrations are decreased.
- Histology specimens may demonstrate changes consistent with progestin effects.

The following laboratory tests may be affected by Medroxyprogesterone Acetate, however the clinical significance is unknown:

- Protein-bound iodine and butanol extractable protein-bound iodine may increase.

- T_3-uptake values may decrease.
- Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX, and X may increase.

- Sulfobromophthalein and other liver function test values may be increased.
- The effects of medroxyprogesterone acetate on lipid metabolism are inconsistent. Both increases and decreases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been observed in studies.

CLINICAL STUDIES

Contraception Studies

In three open label clinical studies, Medroxyprogesterone Acetate (104 mg given every three months subcutaneously), was administered to healthy, sexually-active, nonpregnant women 18 to 49 years of age who desired long-term contraception. In these three studies, no pregnancies were detected among 2042 women treated with Medroxyprogesterone Acetate for up to 1 year. In women less than 36 years of age (at baseline), the Pearl Index pregnancy rate in cycles in which no other contraceptive methods were used, was 0 pregnancies per 100 women-years of use (upper 95% CI = 0.25).

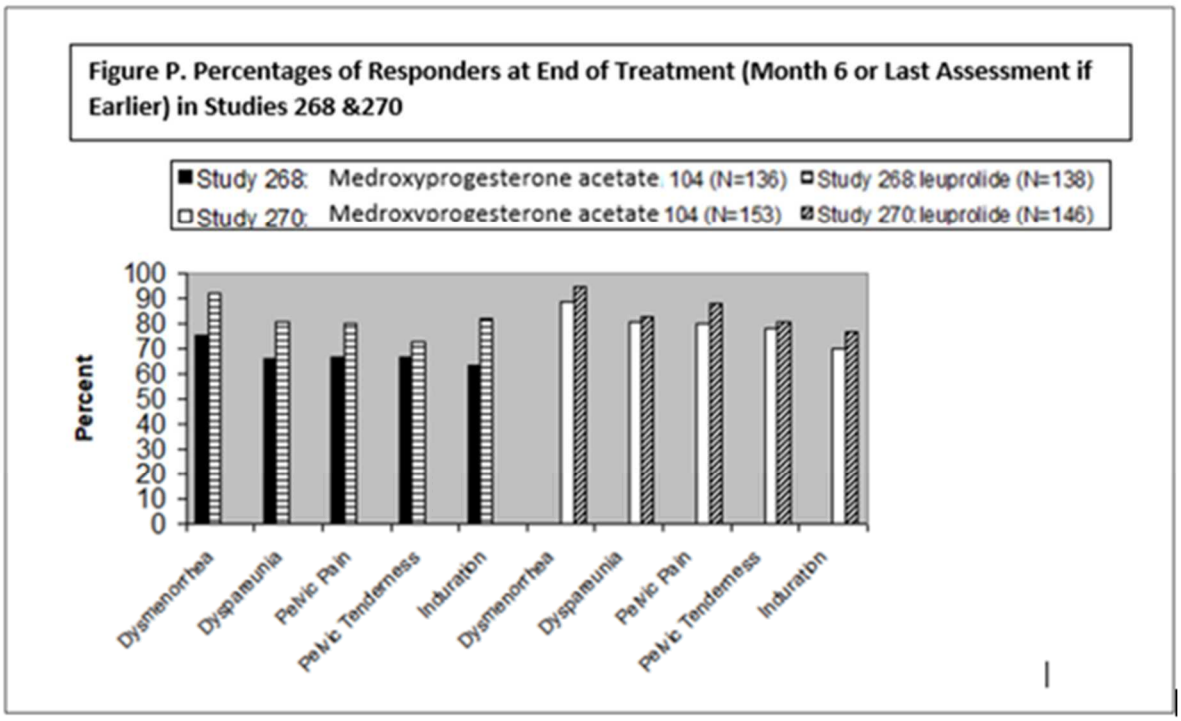
Endometriosis Studies

The efficacy of Medroxyprogesterone Acetate in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in two active comparator-controlled studies in pre-menopausal women 18 to 49 years of age with laparoscopically diagnosed endometriosis and persistent endometriosis pain symptoms (i.e., Studies 268 and 270). Each study assessed endometriosis-associated pain over 6 months of treatment and recurrence of symptoms for 12-months post treatment.

Subjects were treated for six months with Medroxyprogesterone Acetate [104 mg given subcutaneously every 3 months (2 injections)] or leuprolide [11.25 mg given subcutaneously every 3 months (2 injections) or 3.75 mg given subcutaneously every month (6 injections)]. Study 268 was conducted in the U.S. and Canada and enrolled 274 subjects (136 subjects received Medroxyprogesterone Acetate and 138 subjects received leuprolide). Study 270 was conducted in South America, Europe, and Asia, and enrolled 299 subjects (153 subjects received Medroxyprogesterone Acetate and 146 subjects received leuprolide).

Reduction in endometriosis pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (i.e., dysmenorrhea, dyspareunia, and pelvic pain not related to menses) and two signs assessed during pelvic examination (i.e., pelvic tenderness and induration). For each category, a favorable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score (Figure P).

Figure P. Responders at End of Treatment (Month 6 or Last Assessment if Earlier) in Patients with Endometriosis in Studies 268 and 270



Favorable Response = reduction in severity of symptom or sign of ≥1 point on a scale of 0 to 3, as compared to baseline.

Additionally, scores from each of the five categories were combined into a composite score that was considered a global measurement of overall disease improvement. For subjects with baseline scores for each of the 5 categories, a mean decrease of 4 points relative to baseline was considered a clinically meaningful improvement. Across both studies, the mean changes in the composite score met the protocol-defined criterion for improvement for the Medroxyprogesterone Acetate and leuprolide treatment groups.

In the clinical trials, treatment with Medroxyprogesterone Acetate was limited to six months. Data on the persistence of benefit with longer treatment are not available.

Bone Mineral Density in Women Treated with Depo-medroxyprogesterone acetate for Contraception

In a study that compared changes in bone mineral density (BMD) in adult women using Medroxyprogesterone Acetate or DMPA-IM for contraception, both treatments showed BMD reductions in the lumbar spine, total hip, and femoral neck. Mean percent changes in BMD in Medroxyprogesterone Acetate-treated women are shown in Table 2.

Table 2. BMD Mean Percent Change from Baseline in Women Using Medroxyprogesterone Acetate for Contraception

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

BMD Recovery Post-Treatment in Women

Given the similar effects on BMD from Medroxyprogesterone Acetate and DMPA-IM described above, BMD recovery post-treatment is also expected to be similar. In a controlled clinical study that compared changes in BMD in adult women using DMPA-IM for contraception or no hormonal contraception, the 2-year post-treatment follow-up demonstrated incomplete recovery of BMD following the last injection of DMPA-IM. Table 3 shows the change in BMD in women after 5 years of treatment with DMPA-IM and in the control group, as well as the extent of BMD recovery in the subset of women for whom 2-year post-treatment data were available.

Table 3. BMD Mean Percent Change from Baseline in Women by Skeletal Site and Cohort (5 Years of Treatment and 2 Years of Follow-Up)

Time in Study	Spine		Total Hip		Femoral Neck	
	DMPA-IM*	Control**	DMPA-IM*	Control**	DMPA-IM*	Control**
5 years	-5.38% n=33	0.43% n=105	-5.16% n=21	0.19% n=65	-6.12% n=34	-0.27% n=106
7 years	-3.13% n=12	0.53% n=60	-1.34% n=7	0.94% n=39	-5.38% n=13	-0.11% n=63

* Women who received DMPA-IM for 5 years and were then followed for 2 years post-treatment (total time in study of 7 years).

** Women who did not use hormonal contraception and were followed for 7 years.

Bone Mineral Density Changes in Adolescent Females (12 to 18 years of age) Treated with DMPA-IM

The effect of DMPA-IM on BMD in adolescents is described below, and the effect of Medroxyprogesterone Acetate on BMD in adolescents is expected to be similar. The impact of DMPA-IM use for up to 240 weeks (4.6 years) was evaluated in an open-label non-randomized clinical study in 389 adolescent females (12 to 18 years of age). Use of DMPA-IM was associated with a significant decline from baseline in BMD.

Partway through the trial, DMPA-IM administration was stopped (at 120 weeks). The mean number of injections per DMPA-IM user was 9.3. Table 4 summarizes the study findings. The decline in BMD at total hip and femoral neck was greater with longer duration of use. 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%).

Adolescents in the untreated cohort had an increase in BMD during the period of growth following menarche. 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 BMD.

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

Duration of Treatment	DMPA-IM (150 mg)		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 DMPA-IM. Table 5 shows the extent of recovery of BMD up to 60 months post-treatment for adolescents who received DMPA-IM for two years or less compared to more than two years. Post-treatment follow-up showed that, in adolescents treated for more than two years, only lumbar spine BMD recovered to baseline levels after treatment was discontinued. Adolescents treated with DMPA-IM for more than two years did not recover to their baseline BMD level at the femoral neck and total hip even up to 60 months post-treatment. Adolescents in the untreated cohort gained BMD throughout the trial period (see Section 4.4 *Special Warnings and Precautions for Use*).

Table 5. BMD Recovery (Months Post-Treatment) in Adolescents by Years of DMPA-IM Use (2 Years or Less vs. More than 2 Years)

Duration of Treatment (Months)	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%

Bone Fracture Incidence in Women Treated with Depo-medroxyprogesterone acetate for Contraception

A retrospective cohort study to assess the association between DMPA-IM 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 DMPA-IM users and contraceptive users who had no recorded use of DMPA-IM. 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 DMPA-IM use or to other related lifestyle factors that have a bearing on fracture rate.

In the study, when cumulative exposure to DMPA-IM 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 osteoporotic fractures (fracture sites known to be related to low BMD) in the study overall, and the incidence of osteoporotic fractures was not found to be higher in DMPA-IM users compared to non-users.

Importantly, this study could not determine whether use of DMPA-IM has an effect on fracture rate later in life. Given the similar effects on BMD from Medroxyprogesterone Acetate and DMPA-IM described above, bone fracture incidence may also be expected to be similar.

Bone Mineral Density in Women Treated with Medroxyprogesterone Acetate for Endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of Medroxyprogesterone Acetate treatment (104 mg subcutaneously every 3 months) were compared to 6 months of leuprolide treatment (either 11.25 mg given subcutaneously every 3 months or 3.75 mg given subcutaneously every month). Subjects were then observed after treatment completion, for an additional 12 months. See Table 6 for the results.

Table 6. BMD Mean Percent Change from Baseline after Therapy for Endometriosis with Medroxyprogesterone Acetate or Leuprolide for 6 Months, and 6- and 12-Months Post-Therapy (Studies 268 and 270 Combined)

Time of BMD Measurement	Lumbar Spine				Total Hip			
	Medroxyprogesterone Acetate		Leuprolide		Medroxyprogesterone Acetate		Leuprolide	
	N	Mean % Change	N	Mean % Change	N	Mean % Change	N	Mean % Change
Month 6 of treatment (End of Treatment)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months post-treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months post-treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

5.3 Pharmacokinetic Properties

The pharmacokinetic parameters of MPA following a single subcutaneous injection of medroxyprogesterone acetate in healthy women (n=42) are shown in Table 7 and Figure Q.

Table 7. Pharmacokinetic Parameters of MPA after a Single Subcutaneous Injection of DMPA in Healthy Women

	C_{max} (ng/ml)	T_{max} (day)	C_{91} (ng/ml)	AUC_{0-91} (ng·day/ml)	$AUC_{0-\infty}$ (ng·day/ml)	t½ (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

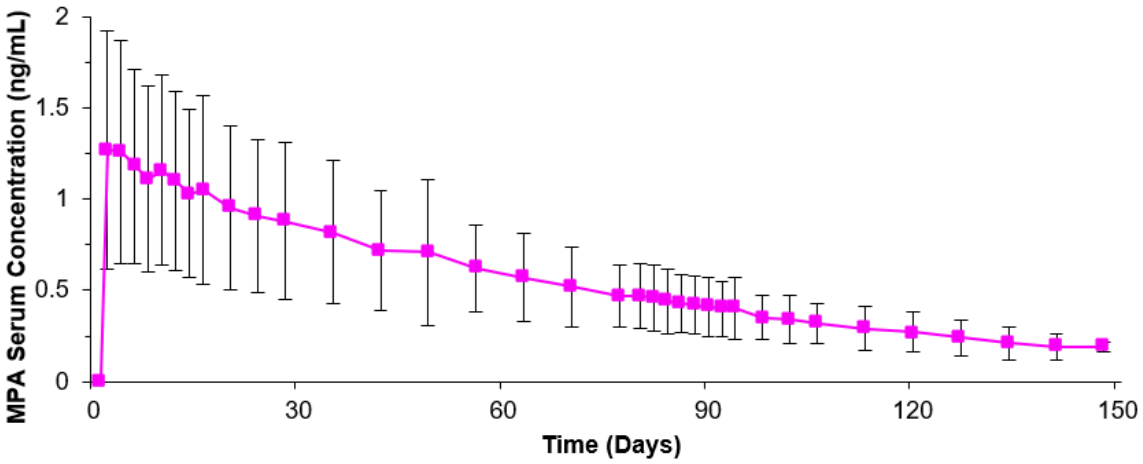
Abbreviations: C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; C_{91}=serum concentration at 91 days; AUC_{0-91} and $AUC_{0-\infty}$= area under the concentration-time curve over 91 days or infinity, respectively; t½ = terminal half-life.

Following subcutaneous administration of single Medroxyprogesterone Acetate doses ranging from 50 to 150 mg (0.48 and 1.4 times the recommended dose, respectively), the AUC and C_{min} (Day 91) increased with higher doses, but there was considerable overlap across dose levels. Serum MPA concentrations at Day 91 increased in a dose proportional manner but C_{max} did not appear to increase proportionally with increasing dose. The AUC data were suggestive of dose linearity.

Absorption

Following a single subcutaneous injection of Medroxyprogesterone Acetate in healthy women, serum MPA concentrations reached ≥0.2 ng/ml within 24 hours. The mean T_{max} was attained approximately 1 week after injection.

Figure Q. Serum Concentration-Time Profile of MPA Mean (SD) after a Single Injection of Medroxyprogesterone Acetate to Healthy Women



In a study to assess accumulation and the achievement of steady state following multiple subcutaneous administrations, trough concentrations of MPA were determined after 6, 12, and 24 months, and in a subset of 8 subjects, bi-weekly concentrations were determined within one dosing interval in the second year of administration. The mean (SD) MPA trough concentrations were 0.67 (0.36) ng/ml (n=157), 0.79 (0.36) ng/ml (n=144), and 0.87 (0.33) ng/ml (n=106) at 6, 12, and 24 months, respectively.

Medroxyprogesterone Acetate was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects of injection site location on the MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection site locations.

Distribution

Plasma protein binding of MPA averages 86%. MPA binding occurs primarily to serum albumin. No binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Elimination

Metabolism

MPA is extensively metabolized in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the first dosing interval (12 to 14 weeks) of Medroxyprogesterone Acetate were generally below 0.5 ng/ml, consistent with its apparent terminal half-life of ~40 days after subcutaneous administration. Most MPA metabolites were excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Specific populations

Racial Groups

There were no significant differences in the pharmacokinetics and/or pharmacodynamics of MPA after subcutaneous administration of Medroxyprogesterone Acetate in African-American, Caucasian, and Asian women.

Effect of Body Weight

Although total MPA exposure was lower in obese women, no dosage adjustment of Medroxyprogesterone Acetate is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA following a single dose was assessed in a subset of women [n=42, body mass index (BMI) ranged from 18.2 to 46.7 kg/m^2]. The AUC_{0-91} values for MPA were 71.6, 67.9, and 46.3 ng·day/ml in women with BMI categories of ≤28 kg/m^2, >28-38 kg/m^2, and >38 kg/m^2, respectively. The mean MPA C_{max} was 1.74 ng/ml in women with BMI ≤28 kg/m^2, 1.53 ng/ml in women with BMI >28–38 kg/m^2, and 1.02 ng/ml in women with BMI >38 kg/m^2, respectively. The MPA trough (C_{min}) concentrations had a tendency to be lower in women with BMI >38 kg/m^2.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

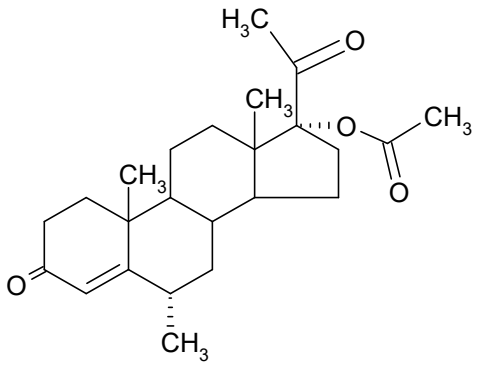
(see Section 4.4 *Special Warnings and Precautions for Use*)

7. DESCRIPTION

SAYANA PRESS is white to off-white homogeneous suspension containing medroxyprogesterone acetate (MPA), a derivative of progesterone, as its active ingredient. MPA is a white to off-white, odorless crystalline powder that is stable in air and that melts between 205ºC and 209ºC. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

The chemical name for MPA is 17-hydroxy-6α-methylpregn-4-ene-3,20-dione 17-

acetate. The structural formula is as follows:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not known

8.2 Shelf-life

36 Months

8.3 Packaging Information

DMPA-SC-Pre-Filled Injection System.

DMPA-SC 104 mg/0.65 ml is packaged in an all in one, pre-fillable single use drug delivery system designed for subcutaneous injection. Prior to use the injection is activated by piercing of the membrane barrier by the double pointed cannula. The dose is then delivered by depressing the unit reservoir. After the dose is expressed, the collapsed reservoir and a one-way valve inhibit refill, preventing re-use.

Each DMPA-SC 104 mg/0.65 ml pre-filled single use injection system is packaged in a foil laminate pouch.

8.4 Storage and Handing Instructions

Store below 30°C.

Medroxyprogesterone Acetate is only for subcutaneous administration and may be administered by a healthcare professional (HCP) or, when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

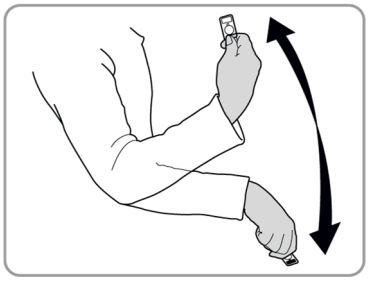
Administration of Medroxyprogesterone Acetate should be initiated under the supervision of a healthcare professional (HCP). After proper training in injection technique and schedule of administration, patients may self-inject with Medroxyprogesterone Acetate if their HCP determines that is it appropriate and with medical follow up as necessary.

INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF SAYANA PRESS

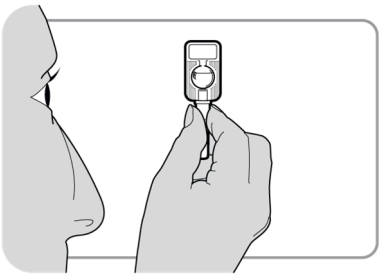
The SAYANA PRESS single-dose container should be at room temperature. It must be vigorously shaken just before use to ensure that the dose being given represents a uniform suspension. The contents are completely sealed inside the reservoir of the injector. The injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid. The dose is administered as a subcutaneous injection (SC) into the anterior thigh or abdomen. When the injection is being given, the injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. **The medication should be injected slowly for 5-7 seconds.**

Mixing the medicine

- Ensure that the SAYANA PRESS single-dose container is at **room temperature**.
- Hold the injector firmly by the port.
- Shake the injector vigorously for at least 30 seconds to mix the medicine.

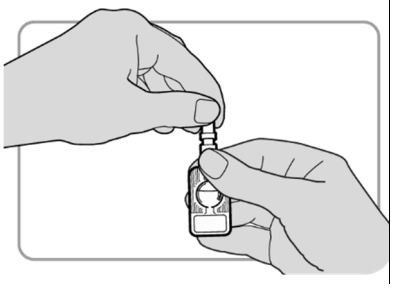


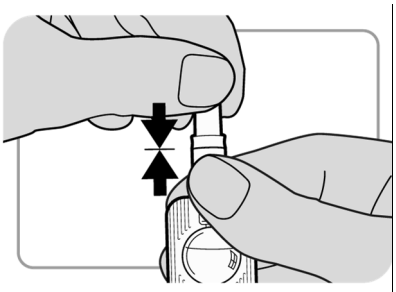
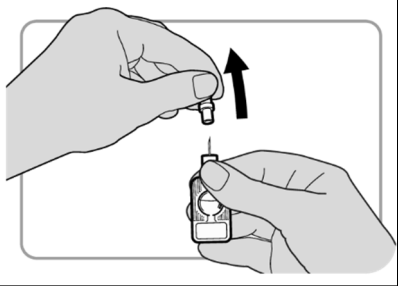
- The medicine should appear white and uniform. If it is not, discard the injector and use a new one.
- If you see liquid leaking out or any other problem, discard the injector and use a new one.
- If there is a delay before injecting, you must repeat the mixing step.



Activating the injector

- Hold the injector firmly by the port, making sure the needle shield is pointing upwards. Take care not to squeeze the reservoir.
- Hold the needle shield with the other hand.



• Push the needle shield firmly towards the port until it will go no further. The injector is now activated.	
• Pull the needle shield off, and discard it.	

Special Precautions for Disposal and Other Handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

9. PATIENT COUNSELLING INFORMATION

Loss of Bone Mineral Density
Advise the patient that the use of Medroxyprogesterone Acetate decreases BMD (see Section 4.4 *Special Warnings and Precautions for Use*).

Arterial and Venous Thromboembolic Disorders
Advise the patient that serious arterial and venous thrombotic events have been seen in women treated with depot medroxyprogesterone acetate (DMPA) (see Section 4.4 *Special Warnings and Precautions for Use*).

Anaphylaxis
Counsel patients on the importance of seeking urgent medical attention if they experience symptoms of anaphylaxis (see Section 4.4 *Special Warnings and Precautions for Use*).

Ectopic Pregnancy
Advise patients to tell their healthcare professional right away if they become pregnant or experience severe abdominal pain to exclude a diagnosis of ectopic pregnancy (see Section 4.4 *Special Warnings and Precautions for Use*).

Bleeding Irregularities
Advise patients at the beginning of treatment that their menstrual cycle may be disrupted, resulting in irregular and unpredictable bleeding or spotting. Explain that bleeding and spotting irregularities usually decrease to the point of amenorrhea as treatment with Medroxyprogesterone Acetate continues, and does not require other therapy (see Section 4.4 *Special Warnings and Precautions for Use*).

Delayed Return of Ovulation and Fertility
Advise patients that return to ovulation and fertility is likely to be delayed after stopping Medroxyprogesterone Acetate (see Section 4.4 *Special Warnings and Precautions for*

Use).

Risks of Breast Cancer
Counsel patients about the possible increased risk of breast cancer in women who use Medroxyprogesterone Acetate (see Section 4.4 *Special Warnings and Precautions for Use*).

Depression
Counsel patients about the possible risk of depression and mood disorders. Advise patients with a history of depression or who are receiving treatment for depression to be alert to any mood changes or worsening of their depression. Counsel patients to follow up with their healthcare professional accordingly (see Section 4.4 *Special Warnings and Precautions for Use*).

Risk of Hyperglycemia in Patients with Diabetes
Advise diabetic patients that some patients receiving progestins may exhibit a decrease in glucose tolerance and hyperglycemia (see Section 4.4 *Special Warnings and Precautions for Use*).

Liver Dysfunction
Advise patients to seek medical advice if they experience symptoms of liver problems such as jaundice (see Section 4.4 *Special Warnings and Precautions for Use*).

Fluid Retention
Counsel patients with conditions that may be influenced by fluid retention to inform their healthcare professional if they experience symptoms of fluid retention (see Section 4.4 *Special Warnings and Precautions for Use*).

Injection Site Reactions
Counsel patients that injection site reactions including site dimpling, scarring or discoloration may occur (see Section 4.4 *Special Warnings and Precautions for Use*).

Sexually Transmitted Infections
Counsel patients that Medroxyprogesterone Acetate does not protect against HIV infection (AIDS) and other sexually transmitted infections (see Section 4.4 *Special Warnings and Precautions for Use*).

Drug Interactions
Counsel patients to contact their healthcare professional if they start a medication that is a CYP3A enzyme inducer (see Section 4.5*Drugs Interactions*). Advise patients that taking a medication that is a CYP3A enzyme inducer may require using a back-up or alternate contraceptive method.

10. DETAILS OF MANUFACTURER

Pfizer Manufacturing Belgium NV,
Rijksweg 12,
Puurs- Sint Amands, 2870, Belgium

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

122-A permission – Import-271/2014 dated 18th Dec 2014 and subsequent permission no. IMP/FF/SND/136/2016 dated 12th Aug 2016.

12. DATE OF REVISION

February 2025