Depo-Provera

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Depo-Provera™
Sterile Aqueous Suspension 50 mg/mL

1. NAME OF THE MEDICINAL PRODUCT

Depo-Provera Sterile Aqueous Suspension 50 mg/mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Depo-Provera Sterile Aqueous Suspension 50 mg/mL: Each mL of injectable suspension contains 50 mg of medroxyprogesterone acetate.

For excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Suspension for intramuscular (IM) injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Medroxyprogesterone acetate (MPA) injectable suspension is indicated for:

Contraception
Contraception (ovulation suppression).

Gynecology
Treatment of endometriosis.
Treatment of menopausal vasomotor symptoms.

Oncology
Adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma.

Treatment of hormonally-dependent, recurrent breast cancer in post-menopausal women.

Long-term Use
Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA injection long-term (see **Section 4.4 Special warnings and precautions for use - Additional Warnings and Precautions for Specific Use or Formulation, *Contraception/Endometriosis - Injectable Formulations*, Loss of Bone Mineral Density (BMD)** and **Section 5.1 Pharmacodynamic properties - *Clinical Studies*, BMD Studies**), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Use in Children
MPA IM is not indicated before menarche.

Data are available in adolescent females (12-18 years) (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies,* BMD Changes in Adolescent Females (12-18 years)**). The safety and effectiveness of MPA IM are expected to be the same for post-menarcheal adolescent and adult females.

4.2 Posology and method of administration

Injectable suspensions should be shaken well before use.

Contraception
Contraception (Ovulation Suppression)
MPA intramuscular injectable suspension should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

Intramuscular (IM)
The recommended dose is 150 mg of MPA injectable suspension every 12-13 weeks (3 months) administered by intramuscular injection in the gluteal or deltoid muscle.

First Injection
The initial IM injection should be given during the first 5 days after the onset of a normal menstrual period; within 5 days post-partum if not breast-feeding; or, if exclusively breast-feeding, at or after 6 weeks post-partum.

Second and Subsequent Injections
If the time interval between IM injections is greater than 13 weeks, pregnancy should be ruled out before administering the next IM injection.

Switching from Other Methods of Contraception
When switching from other contraceptive methods, (MPA IM) should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods.

Gynecology
Use of combined estrogen-progestin therapy in post-menopausal women should be limited to the lowest effective dose and shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically evaluated (see **Section 4.4 Special warnings and precautions for use**).

Periodic check-ups are recommended of a frequency and nature adapted to the individual woman (see **Section 4.4 Special warnings and precautions for use**).

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestin in a woman without an intact uterus.

Endometriosis
Injectable MPA given intramuscularly 50 mg weekly or 100 mg every 2 weeks for at least 6 months.

Menopausal Vasomotor Symptoms
Injectable MPA given intramuscularly 150 mg every 12 weeks.

Oncology
Endometrial and Renal Carcinoma
Injectable MPA 400 mg to 1,000 mg intramuscularly per week is recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilized, it may be possible to maintain improvement with as little as 400 mg per month.

Breast Cancer
Injectable MPA 500 mg/day intramuscularly for 28 days. The patient should then be placed on a maintenance schedule of 500 mg twice weekly as long as she responds to treatment.

Hepatic Insufficiency
No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolized in patients with severe liver insufficiency (see **Section 4.3 Contraindications**).

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

4.3 Contraindications

MPA is contraindicated in patients with the following conditions:
- Known or suspected pregnancy
- Undiagnosed vaginal bleeding
- Severe liver dysfunction
- Known sensitivity to MPA or any component of the drug

Additional Contraindication(s) for Specific Use

Contraception/Gynecology: Known or suspected malignancy of the breast

4.4 Special warnings and precautions for use

General

- Unexpected vaginal bleeding during therapy with MPA should be investigated.

- MPA may cause some degree of fluid retention; therefore, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention.

- Patients with a history of treatment for clinical depression should be carefully monitored while receiving MPA therapy.

- Some patients receiving MPA may exhibit a decreased glucose tolerance. Diabetic patients should be carefully observed while receiving such therapy.

- The pathologist (laboratory) should be informed of the patient's use of MPA if endometrial or endocervical tissue is submitted for examination.

- The physician/laboratory should be informed that use of MPA may decrease the levels of the following endocrine biomarkers:
  a. Plasma/urinary steroids (e.g., cortisol, estrogen, pregnanediol, progesterone, testosterone)
  b. Plasma/urinary gonadotropins (e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH))
  c. Sex-hormone-binding-globulin

- Medication should not be re-administered, pending examination, if there is a 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 not be readministered.

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

- Meningiomas have been reported following long term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Additional Warnings and Precautions for Specific Use or Formulation

Contraception/Endometriosis - Injectable Formulations

Loss of Bone Mineral Density (BMD)

Use of MPA injection reduces serum estrogen levels in premenopausal women and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA injection during adolescence and early adulthood will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be at least partially reversible after MPA injection is discontinued and ovarian estrogen production increases (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies,* BMD Studies**). After discontinuing Depo-Provera injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies*, BMD Studies** - BMD recovery

post-treatment in adolescents).

In adults, BMD was observed for a period of 2 years after MPA injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine. A longer duration of treatment was associated with a slower rate of BMD recovery (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies*, BMD Studies** - BMD Changes in Adult Women). A large observational study of female contraceptive users showed that use of Depo-Provera injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies*, BMD Studies** - Relationship of fracture incidence to use of MPA injectable (150 mg IM) or non-use by women of reproductive age).

BMD Changes in Adult Women after Six Months of Treatment for Endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of MPA-SC treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off-therapy, for an additional 12 months.

The proportion of patients with a decrease of 5% or more in BMD was statistically significantly greater in the leuprolide group compared with MPA-SC at each time point (Table 1).

Table 1. Proportion of Patients with a Decrease of 5% or More from Baseline after 6 Months on Therapy with MPA-SC or Leuprolide and 6 Months after Stopping Therapy (Studies 268 and 270 Combined)

BMD Parameter	MPA-SC n/N* (%)	Leuprolide n/N* (%)	p-value**
End of Treatment (6 Months of Therapy)			
Spine	12/208 (5.8%)	85/229 (37.1%)	<0.001
Total Hip	1/207 (0.5%)	25/227 (11.0%)	<0.001
At 12 Month Visit (6 Months Off-Therapy)			
Spine	8/166 (4.8%)	32/178 (18.0%)	<0.001
Total Hip	3/166 (1.8%)	25/178 (14.0%)	<0.001

* n=number of patients with a decrease in BMD ≥5%; N=total observations.
** Chi-square.

Other birth control methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA injection in women with osteoporotic risk factors, such as:

- Chronic alcohol and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- Low body mass index (BMI) or eating disorder, e.g., anorexia nervosa or bulimia
- Metabolic bone disease
- Strong family history of osteoporosis

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

Contraception

- Most women using MPA injectable suspension experience disruption of menstrual bleeding patterns (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding). As women continue using MPA injectable suspension, fewer experience irregular bleeding and more experience amenorrhea.

- Long-term case-controlled surveillance of users of MPA injectable suspension 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.

- MPA IM injectable suspension has a prolonged contraceptive effect. The median time to conception following the last injection, for those who do conceive is 10 months, with a range of 4 to 31 months, and is unrelated to the duration of use.

- There was a tendency for women to gain weight while on therapy with MPA.

- If jaundice develops, consideration should be given to not readminister the drug.

Sexually Transmitted Infections

Women should be counseled that MPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, MPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Gynecology

Treatment of Menopausal Vasomotor Symptoms/Opposition of Endometrial Effects of Estrogen in Menopausal Women Being Treated with Estrogen (Menopausal Hormone Therapy) - All Formulations:

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of Menopausal Hormone Therapy (MHT) were not studied in the Women's Health Initiative (WHI) trial (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies*, Women's Health Initiative Study**) and, in the absence of comparable data, these risks should be assumed to be similar.

Breast Cancer

The use of combined oral estrogen-progestin by post-menopausal women has been reported to increase the risk of breast cancer. Results from a randomized placebo-controlled trial, the WHI trial, and epidemiological studies (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies***) have reported an increased risk of breast cancer in women taking estrogen-progestin combinations for MHT for several years. In the WHI conjugated equine estrogens (CEE) plus MPA trial and observational

studies, the excess risk increased with duration of use (see **Section 4.2 Posology and method of administration**). The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

A large meta-analysis of observational studies reported that when estrogen plus progestin therapy was taken for more than 5 years, the increased risk of breast cancer may persist for 10 years or more after discontinuation of treatment. The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years. In current users the increased risk of breast cancer in women taking combined estrogen-progestin for MHT becomes apparent after about 1-4 years.

In several epidemiologic studies no overall increased risk for breast cancer was found among users of injectable depot progestogens in comparison to non-users. However, an increased relative risk (e.g., 2.0 in one study) was found for women who currently used injectable depot progestogens or had used them only a few years before. It is not possible to infer from these data whether this increased rate of breast cancer diagnosis among current users is due to increased surveillance among current users, the biological effects of injectable progestogens, or a combination of reasons.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed against the known benefits.

Cardiovascular Disorders

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. Several randomized, prospective trials on the long-term effects (see **Section 4.2 Posology and method of administration**) of a combined estrogen-progestin regimen in post-menopausal women have reported an increased risk of cardiovascular events, such as myocardial infarction, coronary heart disease, stroke, and venous thromboembolism.

- Coronary artery disease

  There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated estrogen and medroxyprogesterone acetate (MPA). Two large clinical trials [WHI CEE/MPA and Heart and Estrogen-progestin Replacement Study (HERS) (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies***)] showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit.

  In the WHI CEE/MPA trial, an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CEE/MPA compared to women receiving placebo (37 vs. 30 per 10,000 person years). The increase in VTE risk was observed in year one and persisted over the observation period (see **Section 4.2 Posology and method of administration**).

- Stroke

  In the WHI CEE/MPA trial, an increased risk of stroke was observed in women receiving CEE/MPA compared to women receiving placebo (29 vs. 21 per 10,000 person-years). The increase in risk was observed in year one and persisted over the observation period (see **Section 4.2 Posology and method of administration**).

- Venous thromboembolism/Pulmonary embolism

  HT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. In the WHI CEE/MPA trial, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism was observed in women receiving CEE/MPA compared to women receiving placebo. The increase in risk was observed in year one and persisted over the observation period (see **Section 4.4 Special warnings and precautions for use**).

Dementia

The Women's Health Initiative Memory Study (WHIMS) (see **Section 5.1 Pharmacodynamic properties - *Clinical Studies***), an ancillary study of WHI, CEE/MPA reported an increased risk of developing probable dementia and mild cognitive impairment (MCI) in post-menopausal women 65 years of age or older. In addition, CEE/MPA therapy did not prevent mild cognitive impairment (MCI) in these women. Use of menopausal hormone therapy (MHT) to prevent dementia or MCI in women 65 years or older is not recommended.

Ovarian Cancer

Current use of estrogen-alone or estrogen plus progestin products in post-menopausal women for five or more years has been associated with an increased risk of ovarian cancer in some epidemiological studies. Past users of estrogen-alone or estrogen plus progestin products were at no increased risk for ovarian cancer. Other studies did not show a significant association. The WHI CEE/MPA trial reported that estrogen plus progestin increased the risk of ovarian cancer, but this risk was not statistically significant. In one study, women who use MHT are at increased risk of fatal ovarian cancer.

History and Physical Exam Recommendation

A complete medical and family history should be taken before the initiation of any hormone therapy. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including cervical cytology.

Gynecology-injectable Formulations

- Prolonged anovulation with amenorrhea and/or erratic menstrual patterns may follow the administration of either a single or multiple injectable dose of MPA.

Oncology

- MPA may produce Cushingoid symptoms.
- Some patients receiving MPA may exhibit suppressed adrenal function. MPA may decrease ACTH and hydrocortisone blood levels.
- The physician/laboratory should be informed that in addition to the endocrine biomarkers listed in **Section 4.4 Special warnings and precautions for use**, the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of adrenal cortex to respond to ACTH should be demonstrated before metyrapone is administered.

Oncology-injectable Formulations

- Prolonged anovulation with amenorrhea and/or erratic menstrual patterns may follow the administration of either a single or multiple injectable dose of MPA.

High Dose Parenteral Formulations (e.g., oncology use in pre-menopausal women)

Decrease in Bone Mineral Density

There are no studies on the bone mineral density (BMD) effects of high doses of parenteral MPA (e.g., for oncology use). However, two clinical studies of adult women of childbearing potential and of adolescent females given Depo-Provera 150 mg IM every three months for contraception, demonstrated significant decreases in BMD (see above - **Loss of Bone Mineral Density (BMD)**). Decreases in serum estrogen due to Depo-Provera may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. It is recommended that all patients have adequate calcium and vitamin D intake. An evaluation of BMD may be appropriate in some patients who use MPA long-term.

4.5 Interactions with other medicinal products and other forms of interaction

Aminoglutethimide administered concomitantly with high doses of oral MPA may significantly depress the serum concentrations of medroxyprogesterone acetate. Users of high-dose oral MPA should be warned of the possibility of decreased efficacy with the use of aminoglutethimide.

Medroxyprogesterone acetate (MPA) is metabolized *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur. Combined use of MPA with CYP3A4 inhibitors or inducers may result in compromised efficacy due to decreased systemic levels of MPA with co-administration of inducers or increased systemic levels of MPA with co-administration of inhibitors.

4.6 Pregnancy and lactation

Pregnancy

MPA is contraindicated in women who are pregnant.

Some reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in fetuses.

Infants from unintentional pregnancies that occur 1 to 2 months after injection of MPA injectable suspension 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 pregnancies while on MPA are uncommon. There is no definitive information for the other formulations of MPA (see **Section 5.2 Pharmacokinetic properties - Distribution**). If the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Lactation

MPA and its metabolites are excreted in breast milk. There is no evidence to suggest that this presents any hazard to the nursing child (see **Section 5.2 Pharmacokinetic properties - Distribution**).

4.7 Effects on ability to drive and use machines

The effect of medroxyprogesterone acetate on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable effects

Contraception

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 4200 women who received MPA for contraception for up to 7 years. Those most frequently (>5%) reported adverse drug reactions were weight increased (69%), weight decreased (25%), headache (16%), nervousness (11%), abdominal pain or discomfort (11%), dizziness (6%), and decrease in libido (6%).

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Immune system disorders			Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Endocrine disorders				Prolonged anovulation
Psychiatric disorders	Nervousness	Depression, Libido decreased	Insomnia	Anorgasmia

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Nervous system disorders	Headache	Dizziness	Seizure, Somnolence	
Vascular disorders			Hot flush	Embolism and thrombosis
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort	Nausea, Abdominal distension		
Hepatobiliary disorders			Liver disorder	Jaundice
Skin and subcutaneous tissue disorders		Alopecia, Acne, Rash	Hirsutism, Urticaria, Pruritus	Lipodystrophy acquired*
Musculoskeletal and connective tissue disorders		Back pain		Arthralgia, Muscle spasms
Reproductive system and breast disorders		Vaginal discharge, Breast tenderness	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Galactorrhea, Pelvic pain	Vaginitis, Amenorrhea, Breast pain
General disorders and administration site conditions		Fluid retention, Asthenia		Pyrexia, Fatigue, Injection site reaction*, Injection site persistent atrophy/indentation/ dimpling*, Injection site nodule/lump*, Injection site pain/tenderness*
Investigations	Weight increased, Weight decreased			Bone density decreased, Glucose tolerance decreased
*ADR identified post-marketing				

Gynecology

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from Phase 3 clinical studies that evaluated efficacy and safety of MPA in gynecology. Those most frequently (>5%) reported adverse drug reactions were dysfunctional uterine bleeding (19%), headache (12%), and nausea (10%):

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Not Known (cannot be estimated from available data)
Immune system disorders		Drug hypersensitivity		Anaphylactic reaction, Anaphylactoid reaction, Angioedema

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Not Known (cannot be estimated from available data)
Endocrine disorders				Prolonged anovulation
Psychiatric disorders		Depression, Insomnia, Nervousness		
Nervous system disorders	Headache	Dizziness		Somnolence
Vascular disorders				Embolism and thrombosis
Gastrointestinal disorders	Nausea			
Hepatobiliary disorders				Jaundice, Jaundice cholestatic
Skin and subcutaneous tissue disorders		Alopecia, Acne, Urticaria, Pruritus	Hirsutism	Lipodystrophy acquired*, Rash
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)	Cervical discharge, Breast pain, Breast tenderness	Galactorrhea	Amenorrhea, Uterine cervical erosion
General disorders and administration site conditions		Pyrexia, Fatigue, Injection site reaction*, Injection site persistent atrophy/indentation /dimpling*	Oedema, Fluid retention, Injection site nodule/lump*, Injection site pain/tenderness*	
Investigations		Weight increased		Glucose tolerance decreased, Weight decreased
*ADR identified post-marketing				

Oncology

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from 1337 patients who received MPA in 4 pivotal studies that evaluated efficacy and safety of MPA for oncology indications.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Frequency Not Known (cannot be estimated from the available data)
Immune system disorders			Angioedema	Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction
Endocrine disorders			Corticoid-like effects		Prolonged anovulation
Metabolism and nutritional disorders		Weight fluctuation, Increased appetite	Diabetes mellitus exacerbated, Hypercalcemia		

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Frequency Not Known (cannot be estimated from the available data)
Psychiatric disorders		Insomnia	Depression, Euphoria, Changes in libido	Nervousness	Confusion
Nervous system disorders		Headache, Dizziness, Tremors		Cerebral infarction, Somnolence	Loss of concentration, Adrenergic-like effects
Eye disorders					Retinal embolism and thrombosis, Cataract diabetic, Visual impairment
Cardiac disorders			Cardiac failure congestive	Myocardial infarction	Tachycardia, Palpitations
Vascular disorders			Thrombophlebitis	Embolism and thrombosis	
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism		
Gastrointestinal disorders		Vomiting, Constipation, Nausea	Diarrhea, Dry mouth		
Hepatobiliary disorders				Jaundice	
Skin and subcutaneous tissue disorders		Hyperhidrosis	Acne, Hirsutism	Alopecia, Rash	Lipodystrophy acquired*, Urticaria, Pruritus
Musculoskeletal and connective tissue disorders			Muscle spasms		
Renal and urinary system disorders					Glycosuria
Reproductive system and breast disorders		Erectile dysfunction	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Breast pain		Amenorrhea, Uterine cervical erosions, Cervical discharge, Galactorrhea
General disorders and administration site conditions		Oedema/fluid retention, Fatigue, Injection site reaction*	Injection site pain/tenderness*	Malaise, Pyrexia	Injection site persistent atrophy/indentation/ dimpling*, Injection site nodule/lump*
Investigations				Glucose tolerance decreased, Blood pressure increased	Liver function test abnormal, White blood cell count increased, Platelet count increased
*ADR identified post-marketing					

Additional Adverse Events Reported During Post-Marketing Experience:

Intramuscular Formulations

In post-marketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients taking MPA IM. There were also cases where a role of IM medroxyprogesterone in the development of injection site atrophy,

necrosis, lipoatrophy, skin atrophy, skin necrosis and injection site ulcer cannot be ruled out.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated.

Overdose treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Medroxyprogesterone acetate (17a-hydroxy-6a-methylprogesterone acetate) is a derivative of progesterone.

Mechanism of Action

MPA is a synthetic progestin (structurally related to the endogenous hormone progesterone) which has been demonstrated to possess several pharmacologic actions on the endocrine system:

- Inhibition of pituitary gonadotropins (FSH and LH).
- Decrease of ACTH and hydrocortisone blood levels.
- Decrease of circulating testosterone.
- Decrease of circulating estrogen levels (as the result of both FSH inhibition and enzymatic induction of hepatic reductase, resulting in increased clearance of testosterone and consequent decreased conversion of androgens to estrogens).

All of these actions result in a number of pharmacological effects, as described below.

Contraception

MPA, when administered parenterally at the recommended dose to women, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and causes thickening of cervical mucus which inhibits sperm entry into the uterus.

Gynecology

Medroxyprogesterone acetate (MPA), administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parenterally administered MPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

Oncology

MPA demonstrates antitumor activity. When MPA is given to patients at high doses (either by the oral route or by IM injection) it is effective in the palliative treatment of hormone-response, malignant neoplasms.

Clinical Studies

BMD Studies

BMD Changes in Adult Women

In a non-randomized controlled clinical study comparing adult women using MPA contraceptive injection (150 mg IM) for up to 5 years to women who elected to use no hormonal contraception, 42 MPA users completed 5 years of treatment and provided at least 1 follow-up BMD measurement after stopping MPA. Among MPA users, BMD declined during the first 2 years of use, with little 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. Spine and hip mean BMD decreases of 5% to 6% among MPA users compared to no significant changes in BMD observed in the control women over the same period of time.

BMD Recovery Post-treatment in Adult Women

In the same study population, there was partial recovery of BMD toward baseline values during the 2-year period after stopping use of MPA injection (150 mg IM).

After 5 years of treatment with MPA injection (150 mg IM), the mean % change in BMD from baseline was -5.4%, -5.2% and -6.1% at the spine, total hip and femoral neck, respectively, while untreated control women, over the same time interval, showed mean changes from baseline of +/- 0.5% or less at the same skeletal sites. Two years after stopping MPA injections, mean BMD had increased at all 3 skeletal sites but deficits remained: -3.1%, -1.3% and -5.4% at the spine, total hip and femoral neck, respectively. At the same time point, women in the control group showed mean changes from baseline BMD of 0.5%, 0.9% and -0.1% at the spine, total hip and femoral neck, respectively.

BMD Changes in Adolescent Females (12-18 years)

The effect of MPA injectable (150 mg IM) use on BMD for up to 240 weeks (4.6 years) was evaluated in an open-label non-comparative clinical study of 159 adolescent females (12-18 years) who elected to begin treatment with MPA; 114 of the 159 participants used MPA continuously (4 injections during each 60-week period) and had BMD measured at Week 60. BMD declined during the first 2 years of use with little change in subsequent years. After 60 weeks of MPA use, mean % BMD changes from baseline were -2.5%, -2.8% and -3.0% at the spine, total hip and femoral neck, respectively. A total of 73 subjects continued to use MPA through 120 weeks; mean % BMD changes from baseline were -2.7%, -5.4% and -5.3% at the spine, total hip and

femoral neck, respectively. A total of 28 subjects continued to use MPA through 240 weeks; mean % BMD changes from baseline were -2.1%, -6.4% and -5.4% at the spine, total hip and femoral neck, respectively.

BMD Recovery Post-treatment in Adolescents

In the same study, 98 adolescent participants received at least 1 MPA injection and provided at least 1 follow-up BMD measurement after stopping MPA use, with MPA treatment for up to 240 weeks (equivalent to 20 MPA injections) and post-treatment follow-up extending for up to 240 weeks after the final MPA injection. The median number of injections received during the treatment phase was 9. At the time of the final MPA injection, BMD % changes from baseline were -2.7%, -4.1% and -3.9% at the spine, total hip and femoral neck, respectively. Over time these mean BMD deficits fully recovered after MPA was discontinued. Full recovery required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck. Longer duration of treatment and smoking were associated with slower recovery. See **Section 4.4 Special warnings and precautions for use – Additional Warnings and Precautions for Specific Use or Formulation, *Contraception/Endometriosis – Injectable Formulations:* Loss of Bone Mineral Density (BMD)**.

Relationship of Fracture Incidence to Use of MPA Injectable (150 mg IM) or Non-use by Women of Reproductive Age

A retrospective cohort study to assess the association between MPA 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 before and after MPA use started and also between MPA users and women who used other contraceptives but had no recorded use of MPA. Among women using MPA, use of MPA was not associated with an increase in fracture risk (incident rate ratio = 1.01, 95% CI 0.92-1.11, comparing the study follow-up period with up to 2 years of observation prior to MPA use). However, MPA users did have more fractures than non-users not only after first contraceptive use (IRR = 1.23, 95% CI 1.16-1.30), but also before first contraceptive use (IRR = 1.28, 95% CI 1.07-1.53).

In addition, fractures at the specific bone sites characteristic of osteoporotic fragility fractures (spine, hip, pelvis) were not more frequent among MPA users compared to non-users (IRR = 0.95, 95% CI 0.74-1.23), nor was there any evidence that longer use of MPA (2 years or more) confers greater risk for fracture compared to less than 2 years of use.

These data demonstrate that MPA users have an inherently different fracture risk profile to non-users for reasons not related to MPA use.

Maximum follow-up in this study was 15 years, therefore, possible effects of MPA that might extend beyond 15 years of follow-up cannot be determined.

Women's Health Initiative Study

The WHI CEE (0.625 mg)/MPA (2.5 mg) trial enrolled 16,608 post-menopausal women aged 50-79 years with intact uteri at baseline, to assess the risks and benefits of

the combined therapy compared with placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (non-fatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. The study was stopped early after an average follow-up of 5.2 years (planned duration 8.5 years) because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index" (see **Section 4.4 Special warnings and precautions for use - Breast Cancer**).

The combination CEE/MPA therapy reported a significant decrease in osteoporotic (23%) and total (24%) fractures.

Million Women Study

The MWS was a prospective cohort study enrolling 1,084,110 women in the UK aged 50-64 years of whom 828,923 with defined time since menopause were included in the main analyses of risk of breast cancer in relation to MHT. Overall, 50% of the study population had used MHT at some point. Most current users of MHT at baseline reported using preparations containing estrogen-alone (41%) or estrogen-progestin combinations (50%). The average duration of follow-up was 2.6 years for analyses of cancer incidence and 4.1 years for analyses of mortality (see **Section 4.4 Special warnings and precautions for use - Breast Cancer**).

Observational Studies of Breast Cancer Risk

A large meta-analysis of observational studies generated evidence for the type and timing of MHT on breast cancer risk. After ceasing MHT, some excess risk persisted for more than 10 years; its magnitude depended on the duration of previous use.

It was reported that, when estrogen plus progestin therapy was taken for more than 5 years, the increased risk may persist for 10 years or more after discontinuation of treatment:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen+progestin	≥10 years	5-9 years	1.19 (1.10-1.28)
	≥10 years	≥10 years	1.28 (1.15-1.43)

The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen+progestin	≥10 years	<1 year	1.06 (0.95-1.19)
	≥10 years	1-4 years	1.09 (1.00-1.18)

In current users, the increased risk of breast cancer in women taking combined estrogen-progestin MHT becomes apparent after about 1-4 years:

MHT type	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	<1 year	1.08 (0.86-1.35)
	1-4 years	1.17 (1.10-1.26)
Estrogen+progestin	<1 year	1.20 (1.01-1.43)
	1-4 years	1.60 (1.52-1.69)

Heart and Estrogen-Progestin Replacement Studies

HERS and HERS II studies were two randomized, prospective secondary prevention trials on the long-term effects of oral continuous combined CEE/MPA (0.625 mg CEE plus 2.5 mg MPA) regimen in post-menopausal women with CHD (see **Section 4.4 Special warnings and precautions for use - Cardiovascular Disorders**). 2,763 post-menopausal women with a mean age of 66.7 years and with intact uteri were enrolled in this study. The average duration of follow-up was 4.1 years for HERS and 2.7 additional years (for a total of 6.8 years) for HERS II (see **Section 4.4 Special warnings and precautions for use - Cardiovascular Disorders**).

Women's Health Initiative Memory Study

The WHIMS, a substudy of WHI, enrolled 4,532 predominantly healthy post-menopausal women age 65 to 79 years to evaluate the effects of CEE/MPA (0.625 mg CEE plus 2.5 mg MPA) or CEE-alone (0.625 mg) on the incidence of probable dementia compared with placebo. The average duration of follow-up was 4.05 years for the CEE/MPA (see **Section 4.4 Special warnings and precautions for use - Dementia**).

5.2 Pharmacokinetics properties

Absorption

Following intramuscular administration, MPA is slowly released, resulting in low, but persistent levels in the circulation. Immediately after intramuscular injection of 150 mg/mL MPA, plasma levels were 1.7 ± 0.3 nmol/L. Two weeks later, levels were 6.8 ± 0.8 nmol/L. Mean time to peak is approximately 4 to 20 days following an intramuscular dose. Serum medroxyprogesterone acetate levels gradually decline and remain relatively constant at about 1 ng/mL for 2-3 months. Circulating levels can be detected for as long as 7 to 9 months following an intramuscular injection.

Distribution

MPA is approximately 90% to 95% protein bound. Volume of distribution is reported as 20 ± 3 liters. Medroxyprogesterone acetate crosses the blood-brain-barrier, and the placental barrier (see **Section 4.6 Pregnancy and lactation**). Low levels of medroxyprogesterone acetate have been detected in breast milk of lactating women (see **Section 4.6 Pregnancy and lactation**) administered 150 mg of medroxyprogesterone acetate by the IM route.

Metabolism

MPA is metabolized in the liver.

Elimination

The elimination half-life following single intramuscular injection is about 6 weeks. Medroxyprogesterone acetate is primarily excreted in the feces, via biliary secretion. Approximately 30% of intramuscular dose is secreted in the urine after 4 days.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term intramuscular administration of medroxyprogesterone acetate (MPA) has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of oral MPA to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays. Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80
Methylparaben
Propylparaben
Polyethylene glycol 3350
Sodium chloride
Water for Injection.

6.2 Incompatibilities

The injectable forms should not be mixed with any other agent.

6.3 Shelf-life

Please refer to EXP date on outer carton.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze. Store vial upright.

6.5 Nature and contents of container

Vial

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal should be observed. Vials and used syringes with attached needle are considered as biohazardous waste and should be discarded in puncture-resistant containers.

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

Depo-Provera-SIN-1024/0
Date of last revision: October 2024

Package leaflet: Information for the patient

Depo-Provera™
Sterile Aqueous Suspension 50 mg/mL
medroxyprogesterone acetate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Depo-Provera is and what it is used for

What Depo-Provera is

Depo-Provera is a medicine that contains medroxyprogesterone acetate, a progestin hormone.

What Depo-Provera is used for

Contraception

Depo-Provera is an injectable form of contraception. It works by inhibiting the hormones that are needed for the release of eggs from your ovaries.

Depo-Provera acts by preventing an egg from fully developing and being released from the ovaries during your menstrual cycle. If an egg is not released it cannot become fertilized by sperm and result in pregnancy. Depo-Provera also causes changes in the lining of your womb that makes it less likely for pregnancy to occur. It also thickens the mucus at the entrance of the womb, making it more difficult for sperm to enter.

Gynecology

Endometriosis

Endometriosis is a condition in which cells from the lining of the uterus (womb) grow in places outside the uterus.

During your period, these cells may grow and break down in the same way as those in the lining of the uterus. This causes pain and discomfort. Depo-Provera helps to stop the growth of cells outside the uterus.

Menopausal vasomotor symptoms

Depo-Provera helps to treat vasomotor symptoms, which occurs during menopause. They include hot flashes, night sweats, heart rate and mood changes, and difficulty sleeping. They are caused by hormonal fluctuations that affect how your body regulates temperature.

Cancer

Depo-Provera is also used in the treatment of certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus). It works by inhibiting the growth of these types of cancer cells. Depo-Provera is not a cure for cancer.

Adolescents (12-18 years)

Depo-Provera is not indicated before menarche. Data in adolescent females (12-18 years) is available. Other than concerns about loss of bone mineral density, the safety and effectiveness of Depo-Provera is expected to be the same for adolescents after menarche and adult females.

Talk with your doctor about whether Depo-Provera is right for you.

2. What you need to know before you use Depo-Provera

Do not use Depo-Provera

Do not start using Depo-Provera if you:

- are allergic to medroxyprogesterone acetate or any of the other ingredients of this medicine listed in section 6.

  If you think you may be allergic, ask your doctor for advice.

- think you may be pregnant.

  If you are pregnant, or think you may be pregnant, do not use Depo-Provera. If your pregnancy test is positive, consult your doctor immediately. Using Depo-Provera during the first trimester of pregnancy may increase the risk of minor defects in your baby.

- have abnormal vaginal bleeding.

- have liver problems.

- any lumps or issues with your breast that have not been diagnosed, including any bleeding or discharge from your nipples.

Warnings and precautions

Talk to your doctor before using Depo-Provera and during your treatment if you experience signs or symptoms described in this section.

Tell your doctor if you:

- have any other medical problems.

  Depo-Provera can cause some fluid accumulation in your body, so your doctor may need to monitor you more closely if you have certain conditions that could be affected by this, such as epilepsy (seizure), migraines, asthma (wheezing), or heart or kidney problems.

- have breast or ovarian cancer.

- have unexpected vaginal bleeding.

- have depression or history of depression.

- have sudden partial or complete loss of vision, or sudden onset of double vision, protrusion of eyeball or migraine.

- dementia.

- have or have ever had a meningioma (a usually benign tumor that forms in the layers of tissue that cover your brain and spinal cord).

Your doctor may take your medical and family history before the prescribing Depo-Provera. Pretreatment and periodic physical examinations, such as blood pressure, breasts, abdomen, and pelvic organs, may also be conducted.

<u>Possible effect on your bones</u>

Depo-Provera works by lowering levels of estrogen and other hormones. However, lower estrogen levels can cause bones to become thinner (by reducing bone mineral density). Premenopausal women who use Depo-Provera tend to have lower bone mineral density than women of the same age who have never used it.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women.

It is unknown if use of Depo-Provera during adolescence and early adulthood will reduce peak bone mass.

The following are risk factors in the development of osteoporosis. You should discuss with your doctor before starting treatment if you have any of the following as an alternative contraceptive may be more suitable to your needs:
- Chronic alcohol and/or tobacco use.
- Chronic use of drugs that can reduce bone mass, e.g., epilepsy medication or steroids.

- Low body mass index or eating disorder, e.g., anorexia nervosa or bulimia.
- Bone disease.
- Strong family history of osteoporosis.

If you use Depo-Provera, it may help your bones if you have an adequate intake of calcium (e.g., in dairy products) and vitamin D (e.g., in oily fish).

Adolescents (12-18 years)

Normally, the bones of adolescents are rapidly growing and increasing in strength. The stronger the bones are when adulthood is reached, the greater the protection against osteoporosis in later life. Since Depo-Provera may cause adolescent bones to become thinner at a time when they should be growing, its effect may be particularly important in this age group. Bones start to recover when Depo-Provera is stopped, but it is not yet known whether the bone mineral density reaches the same levels as it would have if Depo-Provera had never been used.

Use when other contraceptive methods are considered unsuitable or unacceptable, due to unknown long-term effects of bone loss associated with Depo-Provera during the critical period of bone accretion.

You should therefore discuss whether another form of contraception might be more suitable for you with your doctor before starting Depo-Provera.

Possible effect on your periods

Most women using Depo-Provera for contraception will experience a change in their bleeding patterns (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding). As women continue using Depo-Provera, fewer women will experience irregular bleeding, and more will experience little or no bleeding at all.

Possible risks of cancer

Studies found in women who used Depo-Provera for contraception had slight or no increase in overall risk of developing breast cancer, no increase in overall risk of developing cancer of the ovary, liver and cervix, and it shows a prolonged, protective effect of reducing the risk of endometrial cancer.

Other risks

If you develop any of the following, you should consult your doctor before receiving further injections of Depo-Provera:
- Jaundice (yellowing of the skin or eyes).
- Cushingoid symptoms (weight gain with thin extremities, rounded face, fatty lump between shoulders, thin skin that bruises easily, fatigue and muscle weakness).
- Adrenal insufficiency symptoms (extreme tiredness, weak muscles, reduce appetite, fainting, nausea, vomiting, diarrhea, irritability, depression).
- Some women gained weight while using Depo-Provera.

The results of some laboratory tests could also be affected if you are using Depo-Provera so it is important that you tell your doctor.

Sexually transmitted infections

Depo-Provera does not protect against HIV infection, e.g., AIDS, and other sexually transmitted infections.

Safer sex practices, including correct and consistent use of condoms, reduce the transmission of sexually transmitted infections through sexual contact, including HIV.

You should seek advice from your healthcare professional on how to decrease your risk of catching sexually transmitted infections including HIV.

Other medicines and Depo-Provera

Some medicines may affect the way Depo-Provera works. Please tell your doctor about all the medicines you have recently taken, are currently taking, or plan to take, including medicines obtained without a prescription, vitamins, and herbal medicines. The medicines listed in this leaflet may not be the only ones that could interact with Depo-Provera.

The following medicine may reduce the effectiveness of Depo-Provera:

- Aminoglutethimide, a medicine used to treat breast cancer. You may need different amounts of your medicine, or you may need to take different medicines. Your doctor will advise you.

Pregnancy

Do not use Depo-Provera if you are pregnant or suspect you may be pregnant.

Depo-Provera may affect your developing baby if you use it during pregnancy.

Tell your doctor if you think you may have become pregnant during treatment.

Breast-feeding

The hormone in Depo-Provera can pass into your breast milk. There is no evidence to suggest that this presents any hazard to the nursing child.

Driving and using machines

The effect of Depo-Provera on the ability to drive and use machinery has not been systematically studied. If you experience dizziness, drowsiness or tiredness while on treatment with Depo-Provera, take special care when driving or using machines.

3. How to use Depo-Provera

How much is given

Depo-Provera is given as an injection into the muscle of your buttock or upper arm. Your doctor or a trained nurse will give you the injection.

The amount of Depo-Provera and the number of injections that you receive will depend on the reason for the treatment.

The dosage for contraception and for endometriosis is much lower than for cancer.

Contraception

First injection

The recommended dose of Depo-Provera for effective contraception is 150 mg every 12-13 weeks (three months) given as an injection into the muscle of your buttock or upper arm.

Your first injection should only be given during the first 5 days after the start of your normal monthly period.

If you are using Depo-Provera as a form of contraception after the birth of your baby and if you are not breast-feeding, the first injection should be given within 5 days after the baby was born. If you are breast-feeding, the first injection should be given 6 weeks after the baby was born.

Second and subsequent injections

If the time between your injections is greater than 13 weeks, your doctor will need to check that you are not pregnant before they give you another injection.

Switching from other methods of contraception

If you are switching from another form of contraception, then Depo-Provera should be given in a way that ensures you have continuous contraceptive coverage based upon the mechanism of action of both methods.

Gynecology

Use of combined estrogen-progestin therapy in post-menopausal women should be limited to the lowest effective dose and shortest duration. Your doctor will evaluate you periodically and determine the suitable dosage based on your condition.

Unless there is a previous diagnosis of endometriosis, Depo-Provera is not recommended in a woman without an intact uterus.

Endometriosis

The usual dosage is either 50 mg weekly or 100 mg every two weeks.

Treatment for endometriosis is usually for at least 6 months.

Menopausal vasomotor symptoms

The dosage is 150 mg every 12 weeks.

Cancer

Endometrial and renal carcinoma

The initial dosage is 400-1,000 mg per week. If your disease improves and stabilized, your doctor may maintain your dosage as 400 mg per month, which is the lowest effective dosage.

Your doctor will determine how much you should receive and how long you should continue to receive these injections.

Breast cancer

The initial dosage is 500 mg every day for 28 days. After the first 28 days, Depo-Provera is given at 500 mg twice weekly.

Your doctor will determine how much you should receive and how long you should continue to receive these injections.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you experience any of the following serious side effects, seek medical help immediately:

- A serious allergic reaction
  Symptoms include sudden wheezing, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat, skin rash, hives.

- Rapid swelling under the skin (in areas such as the face, throat, arms and legs) which can be life-threatening if throat swelling blocks the airway

- A deep-vein thrombosis (DVT) (a condition in which a blood clot forms in one of your deep veins, usually in your leg)
  Symptoms include:
  - You have severe pain, tenderness or swelling in your calf, ankle or foot

- You have purple discoloration of the skin of the leg or the skin becomes red and warm to touch

- A blood clot in the eye
  Symptoms include loss of vision, pain and swelling of the eye especially if sudden.

- A blood clot in the lungs
  Symptoms include:
  - Sudden, severe, sharp pain in your chest
  - Coughing up blood
  - You suddenly become short of breath
  - Your heart beats more rapidly

- A blood clot in the brain ('a stroke')
  Symptoms include:
  - You have an unusually severe or long headache
  - Your sight is affected in any way
  - You find it difficult to speak
  - You collapse or faint
  - Any part of your body feels weak or numb

- Yellowing of the skin and eyes

- Build-up of bile leading to inflammation of the liver
  Symptoms includes yellowing of the skin and eyes, itching, tiredness and dark colored urine.

Talk to your doctor if you get any other side effects. These can include:

- Allergic reactions
- Ovaries fail to produce eggs
- Nervousness
- Depression
- Changes in sex drive
- Inability to achieve a sexual climax
- Inability to get or keep an erection; impotence
- Difficulty sleeping
- Headache
- Dizziness
- Seizure
- Sleepiness
- Sudden feeling of warmth or heat that spreads over the upper body and face. It is often accompanied by sweating, redness and nervousness
- Abdominal pain, discomfort or bloating
- Nausea
- Liver problems
- Hair loss
- Acne

- Rash
- Itchy rash
- Itching
- Excessive hair
- Changes in the distribution of body fat
- Back pain
- Joint pain
- Muscle spasms
- Changes in vaginal secretions
- Breast tenderness
- Irregular vaginal bleeding or spotting
- Unusual secretion of breast milk when not pregnant or breast-feeding
- Pelvic pain
- Inflammation of the vagina
- Absence of menstruation
- Breast pain
- Swelling, fluid retention
- Weakness
- Fever
- Tiredness
- Injection site reactions (including pain, tenderness, lump, persistent skin indentation/dimpling)
- Weight increased/decreased
- Loss of bone mineral density (a test will be used to diagnose osteoporosis or weak bones)
- Sugar tolerance decreased
- Condition that makes the cervix to appear red and inflamed
- Side effects that mimics of the corticosteroid ingestion
- Increased appetite
- Diabetes mellitus exacerbated
- High blood calcium levels
- Exaggerated feeling of physical and mental well-being
- Confusion
- Involuntary shaking or movement
- Loss of concentration
- Increases heart rate, blood pressure and breathing rate, widened eye pupil, sweating
- Clouding of the lens due to high blood sugar levels
- Vision problems
- The heart does not pump blood as well as it should, with build-up of fluid around the heart, causing shortness of breath, tiredness and ankle swelling
- Heart attack because of blockage in blood supply to a part of the heart
- Rapid heartbeat
- A forceful heartbeat that may be rapid or irregular
- Vomiting
- Constipation
- Diarrhea
- Dry mouth
- Excessive sweating

- Presence of sugar in the urine
- Feeling generally unwell
- Blood pressure increased
- Liver function test abnormal
- White blood cell count increased
- Platelet count increased

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Depo-Provera

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton.

Store this medicine below 30°C. Do not refrigerate or freeze. Store vial upright.

Do not use any pack that is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Depo-Provera contains

- The active substance is medroxyprogesterone acetate.

- The other ingredients are polysorbate 80, methylparaben, propylparaben, polyethylene glycol 3350, sodium chloride, water for injection.

What Depo-Provera looks like and contents of the pack

Depo-Provera is available in a vial.

Depo-Provera-SIN-1223/PIL/0
Date of last revision: December 2023