SAYANA PRESS®

(Medroxyprogesterone acetate)

1. NAME OF THE MEDICINAL PRODUCT

SAYANA PRESS®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Injectable suspension

Depot-medroxyprogesterone acetate (DMPA) 104 mg/0.65 mL injectable suspension is available as a pre-filled syringe or as a pre-filled single-dose injector.

3. PHARMACEUTICAL FORM

Injectable: suspension for subcutaneous (SC) injection.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Contraception

DMPA injectable suspensions (SC) are indicated for:

- Contraception[1]

Gynecology

DMPA injectable SC suspension is indicated for:

- Management of endometriosis-associated pain[99, 100]

Long-term Use

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DMPA 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 **and Section 5.1. – Pharmacodynamic properties - *Clinical Studies*,** Bone Mineral Density Studies), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[80]

Use in Children

DMPA 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 DMPA IM are expected to be the same for postmenarcheal adolescent and adult females.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Sayana Press injectable suspension should be shaken well before use.

Contraception

DMPA subcutaneous (SC) injectable suspensions should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

Subcutaneous (SC)[97,98,118]

The recommended dose is 104 mg. DMPA SC injection must be given by subcutaneous injection into the anterior thigh or abdomen, every 3 months (12–14 weeks). Dosage does not need to be adjusted for body weight, (**see Section 5.2. -Pharmacokinetic properties**). The SC suspension is not formulated for intramuscular injection.

Self-injection[138]:

DMPA SC 104 mg/0.65 mL pre-filled single dose injector may be administered by a healthcare professional (HCP) or, when considered appropriate by the HCP, self-injected by the patient.

Administration of DMPA SC 104 mg/0.65 mL pre-filled single dose injector 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 DMPA SC 104 mg/0.65 mL pre-filled single dose injector if their HCP determines that it is appropriate and with medical follow-up as necessary.

First injection[97,98,118]

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

Second and subsequent injections[97,98,118]

If more than 14 weeks have elapsed since the last SC injection, pregnancy should be ruled out before administering the next SC injection.

Switching from other methods of contraception[97,98,118]

When switching from other contraceptive methods, (DMPA SC) should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of DMPA within 7 days after taking their last active pill).

Gynecology

Use of combined estrogen/progestin therapy in postmenopausal women should be limited to the lowest effective dose[54,82-88] and shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically evaluated.[73,74,75] (**see Section 4.4. – Special warnings and precautions for use.**)

Periodic check-ups are recommended with a frequency and nature adapted to the individual woman.[82,87] (**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.[87,96]

Endometriosis[2,3]

- Injectable DMPA given subcutaneously 104 mg every 3 months for at least 6 months[99,100]

Hepatic Insufficiency[101,118]

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[101,118]

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[66,67,68,69]
- Undiagnosed vaginal bleeding[31]
- Severe liver dysfunction[32]
- Known hypersensitivity to MPA or any component of the drug

Additional Contraindication(s) for Specific Use

Contraception/Gynecology: Known or suspected malignancy of the breast[33]

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

- Unexpected vaginal bleeding during therapy with MPA should be investigated.[31]

- 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.[34]

- 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)[35,36]

    b. Plasma/urinary gonadotrophins (e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH))[36,37]

    c. Sex-hormone-binding-globulin[38,39]

- Medication should not be readministered 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 papilloedema or retinal vascular lesions, medication should not be readministered.[40]

- MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders[41,42,43], 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.

Additional Warnings and Precautions for Specific Use or Formulation

Contraception/Endometriosis - Injectable Formulations

Loss of Bone Mineral Density (BMD)[141]

Use of DMPA 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 DMPA injection during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult[102,118] and adolescent females[103,118], the decrease in BMD during treatment appears to be substantially reversible after DMPA injection is discontinued and ovarian estrogen production increases[80] (**see Section 5.1. – Pharmacodynamic Properties, *Clinical Studies;*** BMD Studies). After discontinuing Sayana Press 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 adolescent women).[142,147]

In adults, BMD was observed for a period of 2 years after DMPA injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (**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 Sayana Press 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 DMPA injectable (150 mg IM) or non-use by women of reproductive age)**.[104,118,141]

BMD Changes in Adult Women after Six Months of Treatment for Endometriosis[99,100,123]

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of DMPA-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 DMPA-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 DMPA-SC or Leuprolide and 6 Months after Stopping Therapy (Studies 268 and 270 Combined)

BMD Parameter	DMPA-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 DMPA 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[80]

It is recommended that all patients have adequate calcium and Vitamin D intake.[76]

Contraception

- Most women using DMPA injectable suspension experience disruption of menstrual bleeding patterns (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding). As

women continue using DMPA injectable suspension, fewer experience irregular bleeding and more experience amenorrhoea.[1]

- Long-term case-controlled surveillance of users of DMPA injectable suspension found slight or no increased overall risk of breast cancer[44,45] and no overall increased risk of ovarian[46], liver[47], or cervical[48] cancer and a prolonged, protective effect of reducing the risk of endometrial[49] cancer.

- DMPA IM injectable suspension has a prolonged contraceptive effect. The median time to contraception 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.[1,50]

- There was a tendency for women to gain weight while on therapy with DMPA.[1,51,52]

- If jaundice develops, consideration should be given to not readminister the drug.[53]

Sexually Transmitted Infections[146,148]

Women should be counseled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA 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.

Breast Cancer

See below.

Gynecology

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

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of Hormone Therapy (HT) 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.[82,88]

Breast Cancer

The use of combined oral estrogen/progestin by postmenopausal women has been reported to increase the risk of breast cancer.[82] 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 HT for several years. In the WHI conjugated equine estrogens (CEE) plus MPA trial and observational studies, the excess risk increased with duration of use[54,82-87] (**see Section 4.2. - Posology and method of administration**). The use of estrogen plus progestin has also been reported to result in an increase in abnormal mammograms requiring further evaluation.[85]

In several epidemiologic studies no overall increased risk for breast cancer was found among users of injectable depot progestogens in comparison to non-users.[105,106,108,119] 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.[44] 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.[105,106,108, 118,119]

Cardiovascular Disorders

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.[82,88] 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 postmenopausal women have reported an increased risk of cardiovascular events such as myocardial infarction, coronary heart disease, stroke, and venous thromboembolism.[54,58,59]

- Coronary Artery Disease

There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated estrogen and medroxyprogesterone acetate (MPA).[54,58,59] 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.[54,58,59,89]

In the WHI CEE/MPA trial, an increased risk of coronary heart disease (CHD) events (defined as nonfatal 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**).[54,89]

- 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**).[54,90]

- 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**).[54,91]

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 probable dementia in postmenopausal women 65 years of age or older.[92,93] In addition, CEE/MPA therapy did not prevent mild cognitive impairment (MCI) in these women. Use of hormone therapy (HT) to prevent dementia or MCI in women 65 years or older is not recommended.[94,109,118]

Ovarian Cancer

Current use of estrogen only 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.[110] Past users of estrogen only or estrogen plus progestin products were at no increased risk for ovarian cancer.[110] Other studies did not show a significant association.[120-122] The WHI CEE/MPA trial reported that estrogen plus progestin increased the risk of ovarian cancer, but this risk was not statistically significant.[111] In one study, women who use HRT are at increased risk of fatal ovarian cancer.[110]

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.[82]

Gynecology-Injectable Formulations

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

Oncology

- MPA may produce Cushingoid symptoms.[57,58,59,60,61]

- Some patients receiving MPA may exhibit suppressed adrenal function. MPA may decrease ACTH and hydrocortisone blood levels.[62,63]

- 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.[64,65]

Oncology–Injectable Formulations

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

Oral Formulations and 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 orally administered MPA or the high doses of parenteral DMPA (e.g., for oncology use). An evaluation of BMD may be appropriate in some patients who use MPA long-term[80], (**see above – Loss of Bone Mineral Density**).

4.5. INTERACTION 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.[72] 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.[125,126] Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.[127]

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy

MPA is contraindicated in women who are pregnant.

Some reports suggest under certain circumstances, an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in fetuses.[66,67]

Infants from unintentional pregnancies that occur 1 to 2 months after injection of DMPA 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 DMPA are uncommon.[67,68,69] There is no definitive information for the other formulations of MPA, (**see Section 5.2. - Pharmacokinetic properties, *Intramuscular formulations:*** 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[70], (**see Section 5.2. - Pharmacokinetic properties, *Intramuscular formulations:*** 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 – Subcutaneous (SC) Formulation:[112,113,139,140]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylactic reaction*, anaphylactoid reaction*, angioedema*, drug hypersensitivity*
Metabolism and nutrition disorders	Fluid retention, increased appetite, decreased appetite
Psychiatric disorders	Depression, insomnia, anxiety[118], emotional disorder, affective disorder, irritability[118], anorgasmia, libido decreased
Nervous system disorders	Migraine, dizziness, headache
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hypertension, varicose veins, hot flush
Gastrointestinal disorders	Abdominal pain, nausea, abdominal distension
Skin and subcutaneous tissue disorders	Alopecia, acne, hirsutism, lipodystrophy acquired*[124,129], dermatitis, ecchymosis, chloasma, rash
Musculoskeletal and connective tissue disorders	Back pain, muscle spasms, pain in extremity
Reproductive system and breast disorders	Menometrorrhagia, metrorrhagia, menorrhagia, ovarian cyst, dysmenorrhoea, amenorrhoea, vaginitis, vaginal discharge,

	dyspareunia[118], pelvic pain, vulvovaginal dryness[118], breast pain, premenstrual syndrome, breast tenderness, breast enlargement
General disorders and administration site conditions	Fatigue, injection-site reaction*, injection site persistent atrophy/indentation/dimpling*, injection site nodule/lump*, injection site pain/tenderness*,[124,129]
Investigations	Hepatic enzyme abnormal, weight increased, smear cervix abnormal, weight decreased
* ADR identified post-marketing	

Please note that in patients taking DMPA IM, there have been reports of anaphylactic responses, thromboembolic events and a few rare cases of osteoporosis including osteoporotic fractures.

Gynecology – Endometriosis-Associated Pain: Subcutaneous (SC) Formulation[99,100,123,135,139]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylactic reaction*, anaphylactoid reaction*, angioedema*, drug hypersensitivity*
Psychiatric disorders	Depression, insomnia, anxiety, affective disorder, irritability, libido decreased
Nervous system disorders	Migraine, dizziness, formication, headache, hypersomnia, paraesthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flush
Gastrointestinal disorders	Nausea, abdominal distension
Skin and subcutaneous tissue disorders	Alopecia, acne, lipodystrophy acquired*, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), metrorrhagia, menorrhagia, ovarian cyst, galactorrhoea, vaginitis, pelvic pain, vulvovaginal dryness, breast pain, breast tenderness
General disorders and administration site conditions	Fatigue, injection-site reaction*, injection site persistent atrophy/indentation/dimpling*, injection site nodule/lump*, injection site pain/tenderness*[124]
Investigations	Weight increased, weight decreased
* ADR identified post-marketing	

Oncology

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylactic reaction, anaphylactoid reaction, angioedema, drug hypersensitivity
Endocrine disorders	Corticoid-like effects, prolonged anovulation
Metabolism and nutritional disorders	Diabetes mellitus exacerbated, hypercalcaemia, weight fluctuation, increased appetite

Psychiatric disorders	Depression, confusion, nervousness, insomnia, euphoria, changes in libido
Nervous system disorders	Cerebral infarction, headache, dizziness, loss of concentration, somnolence, adrenergic-like effects, tremors
Eye disorders	Retinal embolism and thrombosis, cataract diabetic, visual impairment
Cardiac disorders	Cardiac failure congestive, myocardial infarction, tachycardia, palpitations
Vascular disorders	Embolism and thrombosis, thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism
Gastrointestinal disorders	Vomiting, diarrhoea, constipation, nausea, dry mouth
Hepatobiliary disorders	Jaundice
Skin and subcutaneous tissue disorders	Alopecia, acne, hirsutism, lipodystrophy acquired*, urticaria, pruritus, rash, hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscle spasms
Renal and urinary system disorders	Glycosuria
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), amenorrhoea, uterine cervical erosions, cervical discharge, galactorrhoea, breast pain, erectile dysfunction[128]
General disorders and administration site conditions	Oedema/fluid retention, malaise, pyrexia, fatigue, injection-site reaction*, injection site persistent atrophy/indentation/dimpling*, injection site nodule/lump*, injection site pain/tenderness*
Investigations	Glucose tolerance decreased, blood pressure increased, liver function test abnormal, white blood cell count increased, platelet count increased
* ADR identified post-marketing	

4.9. OVERDOSE

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

DMPA, 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.[130]

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 DMPA 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.

Endometriosis

Suppression of serum estradiol concentrations and a possible direct action of DMPA-SC on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.[99,100]

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-responsive, malignant neoplasms.

Clinical Studies

<u>BMD Studies</u>

BMD Changes in Adult Women[77,141]

In a non-randomized controlled, clinical study comparing adult women using DMPA contraceptive injection (150 mg IM) for up to 5 years women who elected to use no hormonal contraception, 42 DMPA users completed 5 years of treatment and provided at least 1 follow-up BMD measurement after stopping DMPA. Among DMPA 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. There were no significant changes in BMD in the control women over the same period of time.

BMD recovery post-treatment in adult women[77,141]

In the same study population, there was partial recovery of BMD toward baseline values during the 2-year period after stopping use of DMPA injection (150 mg IM)[77,118]

After 5 years of treatment with DMPA 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 DMPA 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)[103]

The effect of DMPA 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 DMPA; 114 of the 159 participants used DMPA continuously (4 injections during each 60-week period) and had BMD measured at Week 60. BMD declined during the first 2 years of use with little change in subsequent years. After 60 weeks of DMPA 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 DMPA 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 DMPA 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[142]

In the same study, 98 adolescent participants received at least 1 DMPA injection and provided at least 1 follow-up BMD measurement after stopping DMPA use, with DMPA treatment for up to 240 weeks (equivalent to 20 DMPA injections) and post-treatment follow-up extending for up to 240 weeks after the final DMPA injection. The median number of injections received during the treatment phase was 9. At the time of the final DMPA injection, BMD % changes from baseline were -2.7%, -4.1% and -3.9% at the spine, total hip and femoral neck, respectively. Over time these mean BMD deficits fully recovered after DMPA 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.[147] 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 DMPA injectable (150 mg IM) or non-use by women of reproductive age[141,143,144]

A retrospective cohort study to assess the association between DMPA 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 DMPA use started and also between DMPA users and women who used other contraceptives but had no recorded use of DMPA. Among women using DMPA, use of DMPA 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 DMPA use). However, DMPA 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 DMPA users compared to non-users (IRR = 0.95, 95% CI

0.74-1.23), nor was there any evidence that longer use of DMPA (2 years or more) confers greater risk for fracture compared to less than 2 years of use.

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

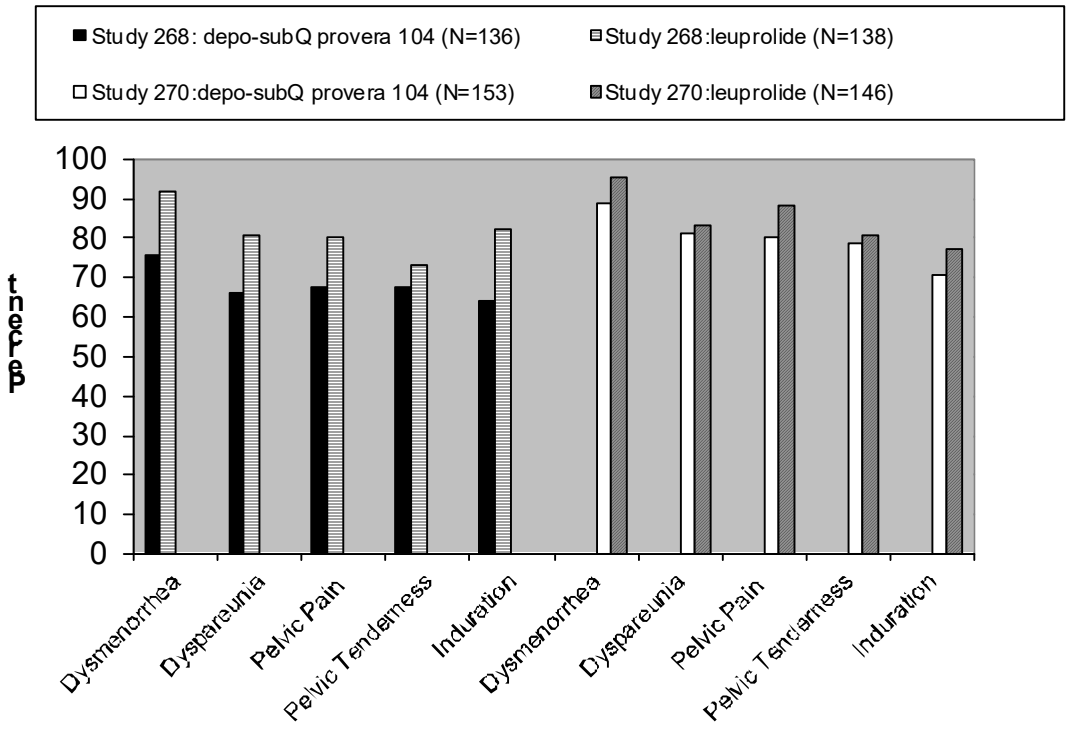
Maximum follow-up in this study was 15 years, therefore, possible effects of DMPA that might extend beyond 15 years of follow-up cannot be determined.

Endometriosis Studies

The efficacy of DMPA-SC in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in two active comparator-controlled studies.[99,100] Each study assessed reduction in endometriosis-associated pain over 6 months of treatment and recurrence of symptoms for 12-months post treatment. Subjects treated with DMPA-SC for 6 months received a 104 mg dose every 3 months (2 injections), while women treated with leuprolide microspheres for 6 months received a dose of 11.25 mg every 3 months (2 injections) or 3.75 mg every month (6 injections). Study 268 was conducted in the USA and Canada and enrolled 274 subjects (136 on DMPA-SC and 138 on leuprolide).[99] Study 270 was conducted in South America, Europe and Asia, and enrolled 299 subjects (153 on DMPA-SC and 146 on leuprolide).[100]

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs assessed during pelvic examination (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 1).

Figure 1. Percentages of Responders at End of Treatment (Month 6 or Last Assessment if Earlier) in Studies 268 & 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, with the total (composite score) 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, for both treatment groups, the mean changes in the composite score met the protocol-defined criterion for improvement.

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

Subjects recorded daily the occurrence and severity of hot flushes. Of the DMPA-SC users, 28.6% reported experiencing moderate or severe hot flushes at baseline, 36.2% at Month 3, and 26.7% at Month 6. Of the leuprolide users, 32.8% reported experiencing moderate or severe hot flushes at baseline, 74.2% at Month 3, and 68.5% at Month 6.

Women's Health Initiative Study

The WHI CEE (0.625 mg)/MPA (2.5 mg) trial[54] enrolled 16,608 postmenopausal 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) (nonfatal 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[86] 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 HT. Overall, 50% of the study population had used HT at some point. Most current users of HT at baseline reported using preparations containing estrogen only (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).

Heart and Estrogen/progestin Replacement Studies

HERS [58] and HERS II [59] 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 postmenopausal women with CHD. (**see Section 4.4. – Special warnings and precautions for use, -** Cardiovascular disorders). 2,763 postmenopausal 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,[92,93] enrolled 4,532 predominantly healthy postmenopausal 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. PHARMACOKINETIC PROPERTIES[98,101,114-116,118]

Subcutaneous formulation

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

Effect of Injection Site

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

Distribution: 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).

Metabolism: MPA is extensively metabolized in the liver.

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

Special populations:

Race

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

Effect of Body Weight

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

5.3. PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term intramuscular administration of medroxyprogesterone acetate (DMPA) 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

Medroxyprogesterone Acetate (MPA)
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Sodium Chloride
Macrogol (Polyethylene Glycol) 3350
Polysorbate 80
Monobasic Sodium Phosphate • 1 H2O
Disodium Phosphate Dodecahydrate
Methionine

Povidone, K17 PF
Sodium Hydroxide or Hydrochloric Acid
Water for injections

6.2. INCOMPATIBILITIES

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

6.3. SHELF LIFE

36 months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at controlled room temperature (15°C-30°C)

6.5. NATURE AND CONTENTS OF CONTAINER

SAYANA PRESS suspension for injection is supplied in a single-dose container in the form of a pre-filled injection system containing medroxyprogesterone acetate injectable suspension 104 mg/0.65 mL. The pack size is one single-dose container.

Sayana Press/LPD/PK-03
According to CDS V 24.0 Dated: 01 November 2019; Supersedes CDS V 23.0 Dated: 17 July 2017

Marketed by:
Pfizer Pakistan Ltd.

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*

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