PT. PFIZER INDONESIA
Local Product Document
Generic Name: Medroxyprogesterone Acetate
Trade Name: PROVERA®
CDS Effective Date: December 01, 2015
Supersedes: January 16, 2009

WARNINGS

CARDIOVASCULAR AND OTHER RISKS

Estrogens with progestins should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) estrogen plus progestin sub study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo.

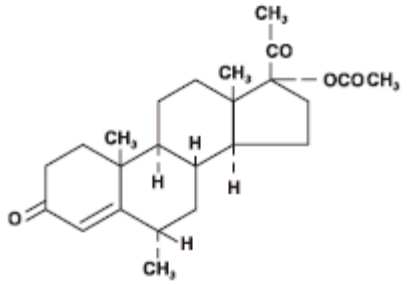
The Women's Health Initiative Memory Study (WHIMS), a sub study of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

PROVERA Tablets contain medroxyprogesterone acetate, which is a derivative progesterone. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-,(6a)-. The structural formula is:



Each PROVERA Tablet for oral administration contains 10 mg medroxyprogesterone acetate.

ACTIONS

Medroxyprogesterone acetate, administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. The drug is progestational agent devoid of estrogenic activity.

Minimal androgenic and anabolic effects may occur. While parenterally administered medroxyprogesterone acetate 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.

Administration with food increases the bioavailability of MPA. A 10 mg dose of oral MPA, taken immediately before or after a meal, increased average MPA C_{max} (51% and 77%, respectively) and average AUC (18 and 33%, respectively). The half-life of MPA was not changed with food.

INDICATION AND USAGE

Secondary amenorrhea, dysfunctional uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer, endometriosis.

CONTRAINDICATIONS

1. Patients with carcinoma of breast of reproductive organs (known or suspected to be estrogen-dependent).
2. Liver diseases of dysfunction.
3. Missed abortion.
4. Suspected pregnancy, should not be used in diagnostic test.
5. Thrombophlebitis, thromboembolic disorders of cerebral apoplexy, or patients with a past history of these conditions.
6. Undiagnosed vaginal bleeding.
7. Known sensitivity to PROVERA tablets.

Additional Contraindication(s) for Specific Use

Contraception/Gynecology*:* Known or suspected malignancy of the breast.

WARNINGS

Before using PROVERA Tablets, the status of the patient should be carefully evaluated.

This evaluation should exclude the presence of genital or breast neoplasia before considering the use of PROVERA.

PROVERA Tablets may cause weight gain and fluid retention. Caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by weight gain or fluid retention.

Some patients receiving PROVERA Tablets may exhibit a decreased glucose tolerance.

The mechanism for this is not known. This fact should be borne in mind when treating all patients and especially known diabetics.

A negative pregnancy test should be demonstrated before starting therapy with PROVERA.

Detectable amounts of PROVERA have been identified in the milk of mothers receiving the drug. The effect of this on nursing infant has not been determined.

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

The age of the patient constitutes no absolute limiting factors although treatment with PROVERA may mask the onset of the climacteric.

The use of PROVERA during the first four months of pregnancy is not recommended.

The physician should be alert to the earliest manifestation of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis).

Should any of these occur or be suspected, the drug should be discontinued immediately.

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.

Additional Warnings and Precautions for Specific Use or Formulation

Breast Cancer

The use of combined 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 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 (see section **DOSAGE AND ADMINISTRATION**). The use

of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

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 reason.

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 **DOSAGE AND 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.

- 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)] showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit.

In the CEE/MPA substudy of WHI, 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).

- Stroke

In the same substudy of WHI, 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 **DOSAGE AND 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 CEE/MPA substudy of WHI, 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 VTE risk was observed in year one and persisted over the observation period.

Dementia

Pooling data from the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, for CEE-alone and CEE/MPA reported an increased risk of developing probable dementia and mild cognitive impairment (MCI) in postmenopausal women 65 years of age or older. Use of HT to prevent dementia or MCI in women is not recommended.

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. Past users of estrogen only 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 HRT 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.

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 Special Warnings and Special Precautions for Use (section **WARNINGS**), 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.

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 MPA (e.g., for oncology use). An evaluation of BMD may be appropriate in some patients who use MPA long-term.

PRECAUTIONS

Patients with a history of treatment for mental depression should be carefully monitored while receiving PROVERA therapy. Some patients may complain of premenstrual like depression while on PROVERA therapy.

Pathologists should be informed of the patients ingestion of PROVERA if endometrial or endocervical tissue is submitted for examination.

The following laboratory tests may be affected by the use of PROVERA: Gonadotropin levels, plasma progesterone levels, urinary pregnanediol levels, plasma testosterone levels (in the male), plasma estrogen levels (in the female), plasma cortisol levels, glucose tolerance test, metyrapone test and sex-hormone-binding-globulin.

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the bioavailability of PROVERA.

The pretreatment physical examination should include special reference to breast and pelvic organs, as well as papanicolaou smear.

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

In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginum, non-functional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination drugs. The mechanism of this decrease is obscure.

For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

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

MPA is metabolized in-vitro primarily by hydroxylation via CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted, inducers and/or inhibitors of CYP3A4 may affect the metabolism of MPA.

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.

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.

Effects on Ability to Drive and Use Machines
The effect of MPA on the ability to drive and use machinery has not been systematically evaluated.

UNDESIRABLE EFFECTS

The following medical events, listed in order of seriousness rather than frequency of occurrence, have been occasionally to rarely associated with the use of progestogens:

1. Anaphylaxis and anaphylactoid-like reactions.
2. Thromboembolic disorders including thrombophlebitis and pulmonary embolism.
3. Central nervous system-nervousness, insomnia, somnolence, fatigue, depression, dizziness, and headache.
4. Skin and mucous membranes-urticaria, pruritus, rash, acne, hirsutism and alopecia.
5. Gastrointestinal-nausea.
6. Breast tenderness and galactorrhea.
7. Miscellaneous-pyrexia, changes in weight and moon faces.
8. Breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, change in weight (increase or decrease), change in cervical erosion and cervical secretions, cholestatic jaundice.

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
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

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)
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,	Galactorrhoea	Amenorrhoea, 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				

OVERDOSE

Overdosage of estrogen plus progestin therapy may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of CE/MPA together with institution of appropriate symptomatic care.

DOSAGE AND ADMINISTRATION

Secondary amenorrhea: 2.5 to 10 mg daily for 5 to 10 days.

Dysfunctional Uterine Bleeding Due to Hormonal Imbalance in the Absence of Organic Pathology: 2.5 to 10 mg daily for 5 to 10 days, starting on the 16th or 21st day of the cycle. Treatment is given for 2 consecutive cycles and then discontinued to see if the dysfunction has regressed. Withdrawal bleeding usually occurs within 3-7 days after discontinuing therapy. Note: For inducing an optimum secretory transformation of an endometrium that has been adequately primed with estrogen therapy, 5-10 mg daily for 10 days starting on the 16th for dysfunctional uterine bleeding.

Endometriosis: 10 mg PROVERA TID for 90 days beginning on cycle day 1. Breakthrough bleeding, which is self-limited, may occur in 30-40% of patients treated. No additional hormonal therapy is recommended for the management of this breakthrough bleeding.

Gynecology
Use of combined estrogen/progestin therapy in postmenopausal women should be limited to the lowest effective dose and shortest duration consistent with treatment goals and risks for individual women, and should be re-evaluated periodically as clinically appropriate (for example, 3-month to 6-month intervals) to determine if treatment is still necessary. (**See section WARNINGS.**)

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 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.

HOW SUPPLIED
PROVERA Tablets are available in the following strengths and package sizes:
10 mg, Boxes of 3 blisters @ 10 tablets; Reg.No.
DKI0054200210C1

Store at maximum temperature 30°C

HARUS DENGAN RESEP DOKTER

Manufactured by:
Pfizer Italia S.r.l., Ascoli, Italy

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia