PT. PFIZER INDONESIA
Local Product Document

Product Document Title: Medroxyprogesterone Acetate
Trade Name: PROVERA®
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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.

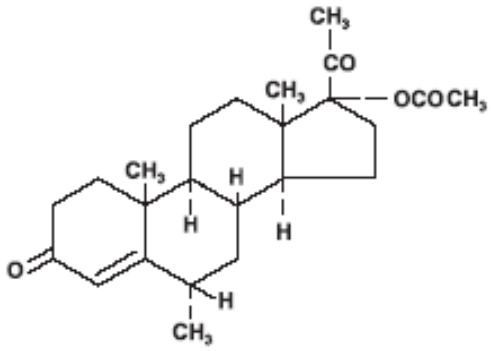
The Women's Health Initiative Memory Study (WHIMS), a sub study of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether 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-,(6)-, The structural formula is:



Each PROVERA tablet for oral administration contains 100 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. The anti-cancer activity of PROVERA at pharmacologic doses in the case of specific forms of hormone-dependent cancers may be due to its effect on the hypothalamic-pituitary-gonadal axis, estrogen receptors and the metabolism of steroids at the tissue level.

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

PROVERA tablets are indicated:
1. As adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma; and
2. In the treatment of hormonally-dependent, recurrent breast cancer in post-menopausal women.

CONTRAINDICATIONS

1. Known sensitivity to medroxyprogesterone acetate.
2. Undiagnosed vaginal bleeding.
3. Undiagnosed urinary tract bleeding.
4. Undiagnosed breast pathology.
5. Liver dysfunction or active liver disease.
6. Thrombophlebitis, thromboembolic disorders or cerebral apoplexy, or patients with a past history of these conditions.

7. Pregnancy (either for diagnosis or therapy), see Warnings.

WARNINGS

PROVERA, especially in the high doses used for cancer therapy, may cause weight gain and fluid retention. With this in mind, 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.

The high doses of PROVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon faces, fluid retention, glucose intolerance, and blood pressure elevation.

In the treatment of carcinoma of breast occasionally cases of hypercalcaemia have been reported.

Any patient who develops an acute impairment of vision, proptosis, diplopia, or migraine headache should be carefully evaluated opthalmologically to exclude the presence of papillo-edema or retinal vascular lesions before continuing medication.

Medroxyprogesterone acetate and/or its metabolites are secreted in breast milk but there is no evidence to suggest that this presents any hazards to the child.

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

The administration of large doses to pregnant women has resulted in the observation of some instances of female foetal masculinisation. Doctors should therefore check that patients are not pregnant before commencing treatment.

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 postmenopausal 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 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 andsex-hormone-binding-globulin.

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

A decrease in glucose tolerance has been observed in some patients on progesterones. The mechanism of this decrease is obscure. For this reason diabetic patients should be carefully observed while receiving progesterone therapy.

Before using PROVERA the general medical condition of the patient should be carefully evaluated.

This product should be used under the supervision of a specialist and the patients kept under regular surveillance.

Occasional uterine bleeding may occur in patient with high dose therapy.

Animal studies show that PROVERA possesses adrenocorticoid activity. This has also been reported in man, therefore patients receiving large doses continuously and for long period should be observed closely.

Treatment with progesterone in the premenopausal patient may mask the onset of the climacteric.

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.

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 and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

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

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, Hypercalcaemia		

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,	Diarrhoea, 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		

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)
Renal and urinary system disorders					Glycosuria
Reproductive system and breast disorders		Erectile dysfunction	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Breast pain		Amenorrhoea, Uterine cervical erosions, Cervical discharge, Galactorrhoea
General disorders and administration site conditions		Oedema /fluid retention, Fatigue		Malaise, Pyrexia	
Investigations				Glucose tolerance decreased, Blood pressure increased	Liver function test abnormal, White blood cell count increased, Platelet count increased
*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

Recurrent endometrial and renal cancer: 200 mg to 400 mg per day.

Recurrent breast cancer in postmenopausal women: 400 to 800 mg per day.

Doses of 1000 mg daily have been given although the incidence of minor side effects, such as indigestion and weight gain, increase with the increase in dose response to hormonal therapy may not be evident until after at least 8 – 10 weeks of therapy.

HOW SUPPLIED
PROVERA tablets are available in the following strengths and package sizes:
100 mg, Boxes of 10 blisters @ 10 tablets; Reg. No. DKI0054200210D1

Store at maximum temperature 30°C

HARUS DENGAN RESEP DOKTER

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

Imported by:
PT. Pfizer Indonesia
PO BOX 2706
Jakarta, Indonesia