PROVERA™

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product name

Provera™

1.2 Strength

5 mg or 10 mg

1.3 Pharmaceutical dosage form

Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative declaration

Medroxyprogesterone acetate (MPA)

2.2 Quantitative declaration

Each tablet contains medroxyprogesterone acetate 5 mg or 10 mg.

3. PHARMACEUTICAL FORM

Tablet

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Gynecology

Medroxyprogesterone acetate tablets are indicated for:

- Treatment of endometriosis
- Treatment of menopausal vasomotor symptoms

- Diagnosis of secondary amenorrhea
- Treatment of secondary amenorrhea
- Treatment of dysfunctional (anovulatory) uterine bleeding from abnormal levels of hormones with no uterus pathology e.g., myoma uteri, uterine cancer
- Opposition of endometrial effects of estrogen in menopausal women being treated with estrogen (menopausal hormone therapy [MHT])

4.2 Posology and method of administration

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 with 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

Oral MPA 10 mg three times per day for 90 consecutive days, beginning on the first day of the menstrual cycle.

Menopausal Vasomotor Symptoms

Oral MPA 10 to 20 mg per day given continuously.

Diagnosis of Secondary Amenorrhea

Oral MPA 2.5 to 10 mg per day for 5 to 10 days.

Treatment of Secondary Amenorrhea

Oral MPA 2.5 to 10 mg daily for 5 to 10 days, for 3 consecutive cycles. In patients with hypotrophy of the endometrium, estrogens should be used concomitantly with MPA therapy.

Dysfunctional (Anovulatory) Uterine Bleeding

Oral MPA 2.5 to 10 mg per day for 5 to 10 days for 2 to 3 cycles and then discontinued to see if the dysfunction has regressed. If bleeding occurs from a poorly proliferative endometrium, estrogens should be used concomitantly with MPA therapy.

Opposition of endometrial effects of estrogen in menopausal women being treated with estrogen (Menopausal Hormone Therapy [MHT])

For women taking 0.625 mg of conjugated estrogen or an equivalent daily dose of another estrogen, MPA can be given in one of two regimens:

- Continuous regimen of MPA - Oral MPA 2.5 to 5.0 mg daily.
- Sequential regimen of MPA - Oral MPA 5 to 10 mg daily for 10 to 14 consecutive days of a 28-day or monthly cycle.

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 hypersensitivity to MPA or any component of the drug.
- 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, epilepsy, asthma, migraine, cardiac or renal impairment 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:
  - Plasma/urinary steroids (e.g., cortisol, estrogen, pregnanediol, progesterone, testosterone)
  - Plasma/urinary gonadotrophins (e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH))
  - 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 re-administered.
- 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

Gynecology

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

Other doses of oral conjugated estrogens with MPA, and other combinations and dosage forms of 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 also 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.

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 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**).

<u>Dementia</u>

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 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. Pre-treatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including cervical cytology.

Decrease in Bone Mineral Density

There are no studies on the bone mineral density (BMD) effects of orally administered MPA. An evaluation of BMD may be appropriate in some patients who use MPA long-term.

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

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 MPA. 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. 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.

4.6 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.

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

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 ≥1/1,000 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
Skin and subcutaneous tissue disorders		Alopecia, Acne, Urticaria, Pruritus	Hirsutism	Rash

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Not Known (Cannot be Estimated from Available Data)
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	Oedema, Fluid retention	
Investigations		Weight increased		Glucose tolerance decreased, Weight decreased

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 progestogen and 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.

Gynecology

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.

Clinical studies

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 sub-study of WHI, enrolled 4,532 predominantly healthy post-menopausal women aged 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

Oral medroxyprogesterone (MPA) is rapidly absorbed with maximum concentration obtained between 2 to 4 hours. The half-life of oral MPA is approximately 17 hours. It is 90% protein bound, and is mainly excreted in the urine.

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.

Distribution

MPA is approximately 90% protein bound, primarily to albumin; no MPA binding occurs with sex-hormone binding globulin. The unbound MPA modulates pharmacologic responses.

Metabolism

Following oral dosing, MPA is extensively metabolized in the liver via ring A and/or side-chain hydroxylation, with subsequent conjugation and elimination in the urine.

At least 16 MPA metabolites have been identified. In a study designed to measure the metabolism of (MPA), the results suggest that human cytochrome P450 3A4 is primarily involved in the overall metabolism of MPA in human liver microsomes.

Elimination

Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates. Mean percent dose excreted in the 24-hour urine of patients with fatty liver as intact MPA after a 10-mg or 100-mg dose was 7.3% and 6.4% respectively. Elimination half-life of oral MPA is 12 to 17 hours.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a carcinogenic effect associated with the oral administration of oral MPA to rats and mice. MPA was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays. MPA 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

Lactose, starch, sucrose, sorbic acid, mineral oil, calcium stearate.

6.2 Incompatibilities

No incompatibility is known for oral formulations.

6.3 Shelf-life

Please see details on carton.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

100 tablets in HDPE bottles

7. MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited, Bangkok, Thailand

8. MARKETING AUTHORIZATION NUMBER

1C 70/59

1C 71/59

9. DATE OF AUTHORIZATION

23 June 2016

10. DATE OF REVISION OF THE TEXT

15 January 2025