1. TRADE NAME(S) OF THE MEDICINAL PRODUCT

PROVERA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg or 10 mg of medroxyprogesterone acetate.

3. PHARMACEUTICAL FORM

Tablets

The scoreline 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 (MPA) tablets are indicated for:
- Treatment of secondary amenorrhea.
- Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

4.2 Posology and Method of Administration

Gynecology
Use of combined estrogen/progestin therapy should be limited to the lowest effective dose and shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically evaluated (see **Section 4.4. Special Warnings and Precautions for Use**).

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

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

Secondary Amenorrhea – MPA may be given in dosages of 5 mg to 10 mg daily for 5 to 10 days. A dose of inducing an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen is 10 mg of MPA daily for 10 days. In cases of secondary amenorrhea, therapy may be started at any time. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing MPA therapy.

Abnormal Uterine Bleeding Due to Hormonal Imbalance in the Absence of Organic Pathology – Beginning on the calculated 16th or 21st day of the menstrual cycle, 5 to 10 mg of MPA may be given daily for 5 to 10 days. To produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen, 10 mg of MPA daily for 10 days beginning on the 16th day of the cycle is suggested. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing therapy with MPA. Patients with a past history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with MPA.

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
- Thrombophlebitis
- Thromboembolic disorders
- Cerebral apoplexy or patients with a past history of these conditions
- Missed abortion
- Known or suspected malignancy of the breast

4.4 Special Warnings and Precautions for Use

General

- Unexpected vaginal bleeding during therapy with MPA should be investigated.
- MPA may cause some degree of fluid retention, therefore, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention.
- Patients with a history of treatment for clinical depression should be carefully monitored while receiving MPA therapy.
- Some patients receiving MPA may exhibit a decreased glucose tolerance. Diabetic patients should be carefully observed while receiving such therapy.

- The pathologist (laboratory) should be informed of the patient's use of MPA if endometrial or endocervical tissue is submitted for examination.
- The physician/laboratory should be informed that use of MPA may decrease the levels of the following endocrine biomarkers:
  a. Plasma/urinary steroids (e.g., cortisol, estrogen, pregnanediol, progesterone, testosterone)
  b. Plasma/urinary gonadotrophins (e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH))
  c. Sex-hormone-binding-globulin
- Medication should not be re-administered, pending examination, if there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilloedema 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.

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**) 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, 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 (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.

Cardiovascular Disorders

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

- Coronary Artery Disease

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

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

- Stroke

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

- Venous thromboembolism/Pulmonary embolism

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

Dementia

Pooling data from the Women's Health Initiative Memory Study (WHIMS) (see **Section 5.1. Pharmacodynamic Properties-Clinical Studies**), a substudy of WHI, for CEE-alone and CEE/MPA reported an increased risk of developing probable

dementia and mild cognitive impairment (MCI) in post-menopausal women 65 years of age or older. Use of HT to prevent dementia or MCI in women is not recommended.

Ovarian Cancer
The CEE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer, but this risk was not statistically significant.

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.

Decrease in Bone Mineral Density
There are no studies on the bone mineral density (BMD) effects of orally administered MPA.

However, a clinical study of adult women of childbearing potential given MPA IM, 150 mg every 3 months, for contraception, demonstrated an average decrease of 5.4% in lumbar spine BMD over 5 years, with at least partial recovery of this bone loss during the first two years after treatment is discontinued. A similar clinical study of MPA 150 mg IM every 3 months in adolescent females, for contraception, demonstrated similar decreases in BMD, which were also more pronounced during the first two years of treatment and which again were at least partially reversible when treatment was discontinued.

Decreases in serum estrogen due to MPA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

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

An evaluation of BMD may be appropriate in some patients who use MPA long-term.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

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

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

4.6 Pregnancy and Lactation

Pregnancy
MPA is contraindicated in women who are pregnant.

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

Infants from unintentional pregnancies that occur 1 to 2 months after injection of MPA injectable suspension may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. The attributable risk is low because pregnancies while on MPA are uncommon. There is no definitive information for the other formulations of MPA.

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/ 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
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*	

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)
Investigations		Weight increased		Glucose tolerance decreased, Weight decreased
*ADR identified post-marketing				

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Overdose treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

Mechanism of Action

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

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

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

Gynecology

Medroxyprogesterone acetate (MPA), administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity.

While parenterally administered MPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily dose.

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**).

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

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

5.2 Pharmacokinetic Properties

Absorption: Oral medroxyprogesterone acetate (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 (SHBG). 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 medroxyprogesterone acetate (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
Long-term intramuscular administration of medroxyprogesterone acetate (MPA) has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of oral

MPA to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays. Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Calcium stearate
Corn starch
Lactose monohydrate
Mineral oil
FD&C Blue No. 2
Aluminum oxide hydrate
Sucrose
Talc

6.2 Incompatibilities

No incompatibility is known for oral formulations.

6.3 Shelf Life

Please refer to expiry date on outer carton.

6.4 Special Precautions for Storage

Store at or below 30°C

6.5 Nature and Contents of Container

Provera Tablets are available in the following strengths and package sizes:
5 mg: Bottles of 100
10 mg: Bottles of 100

6.6 Special Precautions for Disposal and other handling

None

7. PRODUCT OWNER

Pfizer Inc
235 East 42nd Street
New York 10017
United States.

Provera-SIN-1115/0
Date of last revision: November 2015