PROVERA

Table of Content

Please click on either of the following links to access the required information:

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	Oedema, Fluid retention	
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-0522/0
Date of last revision: May 2022

Package leaflet: Information for the patient

PROVERA Tablets 5 mg
PROVERA Tablet 10 mg
medroxyprogesterone acetate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PROVERA is and what it is used for

What PROVERA is

PROVERA is a medicine that contains medroxyprogesterone acetate, a progestin hormone.

What PROVERA is used for

PROVERA is used to treat menstrual periods that have stopped or to treat abnormal uterine bleeding. Talk with your doctor about whether PROVERA is right for you.

2. What you need to know before you take PROVERA

Do not take PROVERA

Do not start taking PROVERA if you:

- are allergic to medroxyprogesterone acetate or any of the other ingredients of this medicine (listed in section 6).

  If you think you may be allergic, ask your doctor for advice.

- have unusual vaginal bleeding.

- had a stroke.

- currently have or have had blood clots.
- have inflammation in a vein leading to a blood clot and blockage.
- currently have or have had liver problems.
- think you may be pregnant.

  PROVERA is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use PROVERA if the test is positive and talk to your doctor. There may be an increased risk of minor birth defects in children whose mothers take PROVERA during the first 4 months of pregnancy.
- had a missed miscarriage.
- have breast cancer or breast lumps not diagnosed by your doctor.

Warnings and precautions

Talk to your doctor before taking PROVERA and during your treatment if you experience signs or symptoms described in this section.

Tell your doctor if you:

- have any other medical problems.

  Your doctor may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis (severe pelvic pain), heart problems, stroke, blood clot in the veins or lungs, kidneys impairment, fluid retention, or decrease in bone mineral density.
- have breast, ovarian or endometrial cancer.
- have unexpected vaginal bleeding.
- have depression or history of depression.
- have sudden partial or complete loss of vision, or sudden onset of double vision, protrusion of eyeball or migraine.
- loss your intellectual function.

Use in children and adolescents

PROVERA is not to be used in children or adolescents (under 18 years of age). Clinical studies have not been conducted in the paediatric population.

Other medicines and PROVERA

Some medicines may affect PROVERA, or be affected by it. Please tell your doctor about all the medicines you have recently taken, are currently taking, or plan to take, including medicines obtained without a prescription, vitamins, and herbal medicines. The medicines listed in this leaflet may not be the only ones that could interact with PROVERA.

The following medicine may reduce the effectiveness of PROVERA:

- Aminoglutethimide, a medicine used to treat breast cancer. You may need different amounts of your medicine or you may need to take different medicines. Your doctor will advise you.

PROVERA with food and drink

Taking PROVERA with food would increase absorption of PROVERA by the body.

Pregnancy

Do not take PROVERA if you are pregnant or suspect you may be pregnant.

PROVERA may affect your developing baby if you take it during pregnancy.

Tell your doctor if you think you may have become pregnant during treatment.

Breast-feeding

The hormone in PROVERA can pass into your breast milk. There is no evidence to suggest that this presents any hazard to the nursing child.

Driving and using machines

The effect of PROVERA on the ability to drive and use machinery has not been systematically studied. If you experience dizziness, drowsiness or tiredness while on treatment with PROVERA, take special care when driving or using machines.

PROVERA contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take PROVERA

Always take this medicine exactly as your doctor has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

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

How much to take

Start at the lowest dose and talk to your doctor about how well that dose is working for you. The lowest effective dose of PROVERA has not been determined. You and your doctor should talk regularly (every 3 to 6 months) about the dose you are taking and whether you still need treatment with PROVERA.

- **Absence of menstrual period:** PROVERA may be given in doses ranging from 5 to 10 mg daily for 5 to 10 days. Three to seven days after you stop taking the tablets you may have bleeding like a period (breakthrough bleeding).

- **Abnormal uterine bleeding:** PROVERA may be given in doses ranging from 5 to 10 mg daily for 5 to 10 days. Three to seven days after you stop taking the tablets you may have bleeding like a period (breakthrough bleeding).

If you take more PROVERA than you should

If you accidentally take too many tablets or a higher dose than you need, contact a doctor for advice right away. If possible, show the doctor the pack, or this leaflet. You may require medical attention.

If you forget to take PROVERA

Take your next dose at your regular time. Do not take a double dose to make up for the forgotten tablets.

If you vomit while taking PROVERA

If you vomit, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

If you stop taking PROVERA

If you are not able to take this medicine as your doctor prescribed or you feel you do not need it anymore, contact your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious. You must immediately contact your doctor if you experience any of those following serious side effects (see also section 2 "What you need to know before you take PROVERA"):

Not known (frequency cannot be estimated from available data)

- Sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness
- Rapid swelling under the skin (in areas such as the face, throat, arms and legs) which can be life-threatening if throat swelling blocks the airway
- Problems due to the formation of blood clots in the blood vessels
- Yellowing of the skin and eyes
- Build-up of bile leading to inflammation of the liver

Reasons for stopping PROVERA treatment immediately

Rarely, PROVERA may cause a severe allergic reaction which can be life-threatening in some cases. You can get some or all of the following symptoms: wheezing, difficulty breathing, feeling faint, swelling of the face or tongue, hands and feet, intense itchy skin rash. If you think you are reacting badly to the medicine, get emergency medical help **immediately**.

If you get any of the following symptoms, you should **stop taking** the tablets and see your doctor **immediately**.

These are symptoms of a **blood clot in the lungs** which may all occur together:

- Sudden, severe, sharp pain in your chest
- Coughing up blood
- You suddenly become short of breath
- Your heart beats more rapidly

These can be symptoms of a **blood clot in the brain ('a stroke')**:

- You have an unusually severe or long headache
- Your sight is affected in any way
- You find it difficult to speak
- You collapse or faint
- Any part of your body feels weak or numb

These are symptoms of a **deep-vein thrombosis (DVT)**:

- You have severe pain, tenderness or swelling in your calf, ankle or foot
- You have purple discoloration of the skin of the leg or the skin becomes red and warm to touch

Talk to your doctor if you get any other side effects. These can include:

Very common (may affect more than 1 in 10 people)

- Irregular vaginal bleeding or spotting
- Headache
- Nausea

Common (may affect up to 1 in 10 people)

- Depression
- Allergic reactions
- Difficulty sleeping
- Nervousness
- Dizziness
- Hair loss
- Acne
- Itchy rash
- Changes in vaginal secretions
- Breast pain
- Breast tenderness
- Fever
- Tiredness
- Weight increased

Uncommon (may affect up to 1 in 100 people)

- Excessive hair
- Unusual secretion of breast milk
- Swelling
- Fluid retention

Not known (frequency cannot be estimated from available data)

- Ovaries fail to produce eggs
- Sleepiness
- Changes in the distribution of body fat
- Rash
- Absence of menstruation
- Ulcers in womb or cervix
- Sugar tolerance decreased
- Weight decreased

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store PROVERA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle.

Store this medicine at or below 30°C.

Do not use any pack that is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What PROVERA contains

- The active substance is medroxyprogesterone acetate. PROVERA tablets come in different strengths
  PROVERA Tablets 5 mg: Each tablet contains 5 mg medroxyprogesterone acetate
  PROVERA Tablets 10 mg: Each tablet contains 10 mg medroxyprogesterone acetate

- The other ingredients are calcium stearate, corn starch, lactose monohydrate, mineral oil, FD&C Blue No. 2, aluminum oxide hydrate, sucrose, and talc.

What PROVERA looks like and contents of the pack

PROVERA Tablets 5 mg are pale blue, round, convex tablets scored on one side and imprinted “PROVERA 5” on the other side; available in bottles of 100 tablets.

PROVERA Tablets 10 mg are white, round, convex tablets scored on one side and imprinted “PROVERA 10” on the other side; available in bottles of 100 tablets.

Provera-SIN-0222/PIL/1
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