PACKAGE LEAFLET

Provera® 2.5 mg Tablets
Provera® 5 mg Tablets
Provera® 10 mg Tablets

Medroxyprogesterone acetate

NAME OF THE MEDICINIAL PRODUCT
Provera 2.5 mg Tablets
Provera 5 mg Tablets
Provera 10 mg Tablets
PHARMACOTHERAPEUTIC CATEGORY
Progestogens - sex hormones and modulators of the genital system.
THERAPEUTIC INDICATIONS
- To oppose stimulation of the endometrium exerted by estrogen when administrated as hormone replacement therapy in menopausal women…
- Functional menometrorrhagia.
- Secondary amenorrhea.

CONTRAINDICATIONS
Medroxyprogesterone acetate (MPA) is contraindicated in patients with the following conditions:
- Known or suspected pregnancy.
- Vaginal bleeding of undetermined nature.
- Severe hepatic insufficiency.
- Hypersensitivity to medroxyprogesterone acetate or any of the excipients.
- Suspected or confirmed breast cancer.
- Confirmed or suspected genital neoplasia at an early stage.

PRECAUTIONS FOR USE
- In case of vaginal bleeding, you should consider non-functional causes. In cases of metrorrhagia of undetermined nature, appropriate diagnostic measures are recommended.
- As progestogens may cause some degree of fluid retention, diseases that could be influenced by this condition should be kept under observation.
- Patients with history of clinical depression should be carefully monitored during treatment with medroxyprogesterone acetate.
- Impaired glucose tolerance was noted in some patients treated with progestogens. For this reason, diabetic patients should be kept under close surveillance during progestogen therapy.
- Pathologists (laboratory) must be informed of the use of medroxyprogesterone acetate by the patient if the endocervical or endometrial tissue is submitted for examination.
- The doctor/laboratory must be aware that the use of medroxyprogesterone acetate may decrease the levels of these endocrine markers:
  a. steroids in plasma/urine (e.g. cortisol, estrogen, pregnandiol, progesterone, testosterone)
  b. gonadotropin in plasma/urine (e.g. LH and FSH)
  c. sex hormone-binding globulin.
- In the event of sudden partial or total loss of sight or in case of exophthalmos, diplopia or migraine, an ophthalmic examination should be done before continuing treatment in order to exclude the presence of papilledema or retinal vascular lesion.
- Medroxyprogesterone acetate was associated with induction of thrombotic or thromboembolic disorders, however, its use is not recommended in patients with a history of venous thromboembolism (VTE). We recommend the discontinuation of treatment with medroxyprogesterone acetate in patients who develop VTE.
- Hepatic insufficiency (see section “Contraindications”)
- Renal insufficiency.

Additional precautions for use:
In the absence of comparable data, the risks identified during the course of the clinical study “Women’s Health Initiative” (WHI) should be considered similar to other oral dosages of conjugated estrogen with medroxyprogesterone acetate and in case of other combinations and pharmaceutical forms related to hormonal therapy.
Breast cancer
An increased risk of breast cancer was reported following the use of oral estrogen-progestogen combinations, in postmenopausal women. The results derived from a randomized, placebo-controlled clinical trial, the WHI clinical trial and epidemiological studies have reported an increased risk of breast cancer in women taking hormonal therapy like estrogen-progestogen combination for several years. The excess risk increases with duration of use, as revealed by the WHI study, conjugated equine estrogens (CEE) plus MPA trial, and observational studies. An increased mammographic abnormalities was also reported with the use of estrogen plus progestogen, requiring further evaluation.
Cardiovascular diseases
Estrogen alone or in association with progestogens should not be taken for the prevention of cardiovascular disease. Several randomized, prospective studies on long-term effects (see “Dose, method and time of administration”) of a combined treatment with estrogen-progestogen in postmenopausal women, showed an increased risk of cardiovascular events such as myocardial infarction, coronary artery disease, stroke and venous thromboembolism.
- Coronary Heart Disease
  There is no evidence from randomized, controlled clinical studies, of cardiovascular benefits arising from the continuous use of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA).
  Two expanded clinical studies (WHI CEE/MPA and Heart and Estrogen/progestogen Replacement Study-HERS) showed a possible increased risk of cardiovascular morbidity in the first year of treatment and without an overall benefit.
  In the WHI CEE/MPA study, an increased risk of coronary events was observed (defined as non-fatal myocardial infarction and fatal coronary heart disease) in women taking CEE/MPA, compared to those receiving placebo (37 vs. 30 per 10.000 persons per year). An increased risk of venous thromboembolism has been observed in the first year of treatment that persisted throughout the period of observation (see “Dose, method and time of administration”).
- Stroke
  In the WHI CEE/MPA study, an increased risk of stroke was observed in women taking CEE/MPA compared to those receiving placebo (29 vs. 21 for 10.000 persons per year). The increased risk was observed in the first year of treatment and persisted throughout the period of observation (see “Dose, method and time of administration”).
- Venous thromboembolism /Pulmonary embolism
  Hormone therapy is associated with a higher relative risk of venous thromboembolism, i.e. deep venous thrombosis or pulmonary embolism. In the CEE/MPA substudy of WHI, a double frequency of venous thromboembolism including deep venous thrombosis and pulmonary embolism was observed in women taking CEE/MPA compared to those receiving placebo. The increased risk was observed during the first year of treatment and persisted throughout the period of observation (see “Dose, method and time of administration”).

Dementia
The Women’s Health Initiative Memory Study (WHIMS), an ancillary study of WHI, relating to the administration of CEE/MPA, showed an increased risk of probable dementia and mild cognitive disorder in postmenopausal women of age equal or greater than 65 years. Additionally, the CEE/MPA based therapy didn’t prevent the mild cognitive impairment (MCI) in these women. The use of hormone therapy (HT) to prevent dementia or mild cognitive disorder is not recommended in women of age equal or greater than 65 years.
Ovarian Carcinoma
Some epidemiological studies have observed that current use of estrogen-based products alone or estrogen plus progestogen in postmenopausal women for five or more years was associated with an increased risk of ovarian cancer. Patients who have previously used estrogen-based products alone or estrogen plus progestogens showed no increased risk of ovarian cancer. Other studies showed no significant association. The WHI CEE/MPA study showed that estrogen plus progestogens increases the risk of ovarian cancer, but this risk is not statistically significant. In one study, women who used hormone replacement therapy showed an increased risk of fatal ovarian cancer.
Recommendations on the history and physical examination
A complete history should be taken before the start of any hormonal therapy. Physical examination prior to treatment and periodically should pay particular attention to blood pressure, pelvic organs, breasts and abdomen, including cervical cytological analysis.
INTERACTIONS
Inform your doctor or pharmacist if you have recently taken any other medicines, including medicines obtained without a prescription.
The concomitant administration of Provera with aminoglutethimide may significantly depress the bioavailability of Provera.
SPECIAL WARNINGS
Before prescribing Provera, the presence of mammary or genital neoplasm should be excluded.
The physician should pay attention to the early manifestations of thromboembolic disorders and should suspend the treatment with Provera if you encountered such episodes or on mere suspicion.
Before initiating or resuming hormone replacement therapy (HRT), besides performing general physical and gynecological examination, the patient’s personal and family history should be assessed, in the light of contraindications, special warnings and precautions for use. Physical examination before treatment and later periodic examination shall include these particular tests: blood pressure, breast, abdomen and pelvic organs, including cervical cytology.
During treatment, it is recommended to adapt the nature and frequency of the periodic specialized checks to the patient and to conduct repeated visits for breast examination and/or mammogram together with control programs recommended for healthy women, modified according to their individual clinical needs.
Currently available clinical data (derived from the assessment of the data emerged from both the randomized placebo-controlled WHI-Women’s Health Initiatives, and fifty-one epidemiological studies) suggest that in postmenopausal women who are undergoing or have undergone hormone replacement therapy, there is a mild to moderate increase in the likelihood of diagnosis of breast cancer. This may be due to early diagnosis in treated patients, or a real effect of HRT, or the combination of both.
The likelihood of the diagnosis of breast cancer increases with the duration of treatment and seems to return to the initial value five years after discontinuation of HRT. Breast cancer diagnosed in patients who use or have recently used HRT would seem less invasive in nature than that found in untreated women.
In women aged between fifty and seventy years, not using HRT, breast cancer is diagnosed in approximately forty-five per thousand persons, with an increase related to age.
It has been estimated that in women who use HRT, for at least five years, the number of additional cases of diagnosis of breast cancer will be between two and twelve per thousand persons, depending on the age at which patients begin treatment and the duration of treatment.
It is important that the doctor discusses the increased likelihood of diagnosis of breast cancer with patients assigned to long-term therapy, and evaluating it against benefits of HRT.
Patients with family history of cancer and those who suffer or have suffered from the following diseases should be closely monitored:
- Recurrent cholestasis or persistent itching during pregnancy
- Alterations of liver function
- Renal or cardiac insufficiency
- Breast nodules or fibrocystic mastopathy
- Epilepsy
- Asthma
- Otospongiosis
- Diabetes mellitus
- Multiple sclerosis
- Systemic lupus erythematosus

Pregnancy and Lactation
Pregnancy
Ask your doctor or pharmacist before taking any medicine
Medroxyprogesterone acetate is contraindicated in pregnant women.
Some data suggest a possible relationship between the administration of progestogens in the first trimester of pregnancy and the presence of congenital genital malformation in fetus in special circumstances.
The patient should be informed of the potential risk to the fetus if she got pregnant while using this medication.
Lactation
Medroxyprogesterone acetate and its metabolites are excreted in breast milk. There is no evidence to suggest that this represents a risk to the infant.
Effects on the ability to drive and to use machines
No known data about it.
Reduction of bone mineral density
There are no studies on the effects of medroxyprogesterone acetate on bone mineral density reduction when administered orally.
However, a clinical study on adult females of childbearing age who were treated with 150 mg of medroxyprogesterone acetate every 3 months intramuscularly for contraception, has demonstrated a 5.4% decrease of bone mineral density of lumbar spine in 5 years, with at least a partial recovery of bone density during the first two years after discontinuation of treatment. A similar clinical study on adolescent females, who have been treated with 150 mg of medroxyprogesterone acetate every 3 months intramuscularly for contraception, showed similar reductions of bone mineral density, which were even more pronounced during the first two years of treatment and that, even in this case, were at least partially reversible once treatment stopped. The reduction of serum levels of estrogen due to medroxyprogesterone acetate may entail a reduction in bone mineral density in premenopausal women and may increase the risk of osteoporosis in old age.
Taking an adequate amount of calcium and vitamin D is recommended for all patients.
Evaluation of bone mineral density in those patients taking medroxyprogesterone acetate for long-term treatment would be also appropriate.
Important information about some of the excipients
This medicine contains **lactose** so if you were diagnosed by an intolerance to some sugars, contact your doctor before taking this medicine.
DOSE, METHOD AND TIME OF ADMINISTRATION
The use of estrogen-progestogen combined therapy in post-menopausal women should be limited to the lowest effective dose and should be of minimum duration considering both, treatment objectives and risks to each patient and should be evaluated periodically (see “Precautions of use” and “Special Warnings”).
Periodic examinations are recommended, with frequency and type adapted to each patient (see “Special Warnings”).
Unless there is a previous diagnosis of endometriosis, the addition of a progestogen is not recommended in women without a uterus.
- **To oppose stimulation of the endometrium exerted by estrogen when administrated as hormone replacement therapy in menopausal women**: from 5 to 10 mg/day for at least 10 days starting from the 11th day of the cycle that involves an estrogen therapy, for 21 days. Withdrawal bleeding occurs usually within 3-7 days after discontinuation of treatment with Provera.
- **Functional menometrorrhagia:** initial doses of 5 to 10 mg/day for 10 days should gradually establish cessation of bleeding, during the course of treatment. Withdrawal bleeding occurs within 3-7 days after discontinuation of treatment with Provera.
  The treatment with Provera at doses of 5-10 mg/day for 10 days can be repeated, starting the administration at the 16th day of the cycle, for 2-3 cycles. Subsequently, discontinue therapy to test regression of dysfunction.
- **Secondary amenorrhea**: from 5 to 10 mg/day, for 10 days. If the endometrium has been previously stimulated by adequate rates of endogenous estrogens, withdrawal bleeding occurs within 3-7 days after discontinuation of treatment with Provera.

OVERDOSE
In case of ingestion/accidental intake of an overdose of Provera, immediately call your doctor or contact your nearest hospital.
If you have any questions on the use of Provera, contact your doctor or pharmacist.
Oral doses exceeding 3g per day are well tolerated. In case of overdose, treatment should be symptomatic and supportive.
SIDE EFFECTS
Like all medicines, Provera may cause side effects although not everybody gets them.

Immune system disorders	hypersensitivity reactions (e.g. anaphylaxis or anaphylactoid reactions, angioedema)
Endocrine disorders	prolonged anovulation
Metabolism and nutritional disorders	fluid retention/edema, weight changes
Psychiatric disorders	depression, insomnia, nervousness
Nervous system disorders	drowsiness, dizziness and migraine
Vascular disorders	thromboembolic disorders
Gastrointestinal disorders	nausea
Hepatobiliary disorders	cholestatic jaundice/jaundice
Skin and subcutaneous tissue disorders	hives, itching, rash, acne, hirsutism and alopecia
Reproductive system and breast disorders	abnormal uterine bleeding (irregular, increase, decrease), amenorrhea, cervical erosion, breast pain and galactorrhea
General Disorders and administration site disorders	Fatigue, fever, weakness
Diagnostic investigation	alterations of cervical secretions, decreased glucose tolerance

Compliance with the instructions contained in the leaflet reduces the risk of side effects.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.
EXPIRATION AND STORAGE
Expiration: see the expiration date printed on the package.
CAUTION: Do not use this medicine after the expiration date printed on the package.
The expiry date refers to the product in correctly stored intact packaging.
Do not store above *30 °C*
Keep this medicine out of reach and sight of children
COMPOSITION
Provera 2.5 mg Tablets
1 Tablet contains:
Active ingredient: medroxyprogesterone acetate 2.5 mg.
Excipients: lactose monohydrate, talc, maize starch, sucrose, calcium stearate, liquid paraffin, E110.
Provera 5 mg Tablets
1 Tablet contains:
Active ingredient: medroxyprogesterone acetate 5 mg.
Excipients: lactose monohydrate, talc, maize starch, sucrose, calcium stearate, liquid paraffin, E132, hydrated aluminum oxide.
Provera 10 mg Tablet
1 Tablet contains:
Active ingredient: medroxyprogesterone acetate 10 mg.
Excipients: lactose monohydrate, talc, maize starch, sucrose, calcium stearate, liquid paraffin.
PHARMACEUTICAL FORM AND CONTENTS
Tablets for oral use.
Provera 2.5 mg Tablets, packs of 20 tablets.
Provera 5 mg Tablets, packs of 12 and 24 tablets.
Provera 10 mg tablets, packs of 12 and 25 tablets.
Not all pack sizes may be marketed.
MARKETING AUTHORIZATION HOLDER
Pfizer Italy S.r.l. - via Isonzo, 71-04100 Latina
MANUFACTURER AND FINAL CONTROLLER
Produced, packaged and checked by:
- Provera 2.5 and 10 mg Tablets: Pfizer Italy S.r.l - Location Marino del Tronto 63100 - Ascoli Piceno (AP)
- Provera 5 mg Tablets: Pfizer Italy S.r.l. - Location Marino del Tronto 63100 - Ascoli Piceno (AP)

REVISION OF THE LEAFLET BY THE ITALIAN MEDICINES AGENCY
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