

PRODUCT MONOGRAPH

Pr^rpms-MEDROXYPROGESTERONE
(Medroxyprogesterone acetate Tablets USP)

2.5mg, 5 mg and 10 mg

Progestin

PHARMASCIENCE INC..
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PRODUCT MONOGRAPH

Pr **pms-MEDROXYPROGESTERONE**

(Medroxyprogesterone acetate Tablets USP)

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PHARMACOLOGICAL CLASSIFICATION

Progestin

Warning

As the Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep venous thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens and medroxyprogesterone acetate compared to those receiving placebo tablets, the following should be highly considered:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogen with or without progestins should be prescribed for **the shortest period** possible for the recognized indication.

ACTION AND CLINICAL PHARMACOLOGY

pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate) is an orally active progestational steroid (progestin) derived from a natural source (soybeans). When administered to women with adequate levels of estrogen (endogenous or exogenous), pms-MEDROXYPROGESTERONE transforms a proliferative endometrium into a secretory endometrium. Furthermore, the anti-cancer activity of pms-MEDROXYPROGESTERONE at pharmacologic doses, may be dependent on its effect on the hypothalamic/ pituitary/ gonadal axis, estrogen receptors and metabolism of steroids at the tissue level.

Clinical Pharmacology

Medroxyprogesterone acetate is a progestational agent devoid of androgenic and estrogenic activity.

Endocrine:

In appropriate doses, medroxyprogesterone acetate suppresses the secretion of pituitary gonadotropins which in turn, prevents follicular maturation, producing anovulation in the reproductive aged woman.

Medroxyprogesterone acetate, like progesterone, is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be observed.

Suppression of the Leydig cell function in the male (i.e. suppresses endogenous testosterone production) occurs after appropriate doses of medroxyprogesterone acetate.

Reproductive Tract:

Medroxyprogesterone acetate, when administered to women with adequate levels of estrogen (endogenous or exogenous), transforms a proliferative endometrium into a secretory endometrium. Withdrawal bleeding is anticipated within 7 days after stopping medroxyprogesterone acetate.

Microscopically, the secretory change is associated with glycoprotein-rich stromal cells which surround the glands and vessels and assist them in maintaining their integrity during hormonal withdrawal. The result is an orderly regression and remodelling, and preservation of the functional layer of the endometrium.

Medroxyprogesterone acetate decreases both cytoplasmic and nuclear estrogen receptors in endometrial cells. In addition, medroxyprogesterone acetate induces estradiol dehydrogenase (E₂DH) activity, the enzyme mechanism by which endometrial cells metabolize and excrete estrogens. Medroxyprogesterone is added for protection against endometrial hyperplasia during long-term estrogen therapy of women with intact uteri.

Oral medroxyprogesterone acetate also produces typical progestational changes in the cervical mucous (inhibits ferning) and increases the intermediate cell count in the maturation index of the vaginal epithelium.

Skeletal system:

Presently there are no conclusive data concerning the mechanism of action of progestins on bone.

Clinically, research to date has shown women treated with medroxyprogesterone acetate to prevent estrogenic hyperstimulation of the endometrium do not lose protection against osteoporosis .

Cardiovascular: There is no conclusive evidence that medroxyprogesterone acetate produces adverse coagulation changes in women receiving the progestin alone, or as part of a sequential regimen with estrogen.

Research indicates that medroxyprogesterone acetate has little, if any, adverse effect on blood pressure. Results from studies show no significant difference between estrogen-treated and estrogen-medroxyprogesterone acetate-treated patients for the development of hypertension.

Medroxyprogesterone acetate shows small or undetectable effects on lipoproteins when used at therapeutic dosages. Furthermore, research demonstrates that the use of medroxyprogesterone acetate with estrogen in hormone replacement therapy maintains the estrogenic effects on lipid profile.

Metabolic:

In studies which examined metabolic changes, a decrease in glucose tolerance has been associated with progestins, including medroxyprogesterone acetate.

Pharmacokinetics of pms-MEDROXYPROGESTERONE

Medroxyprogesterone acetate has an apparent half-life of approximately 30 hours.

Medroxyprogesterone acetate is rapidly absorbed from the gastrointestinal tract and metabolized in the liver to several progestin metabolites. The major drug-related material found in circulation following oral administration has been characterized as both free and glucuronide-conjugated metabolites of medroxyprogesterone acetate.

Medroxyprogesterone acetate is primarily eliminated via fecal excretion, to which biliary secretion may contribute. Approximately 44% of an oral dose is eliminated through urinary excretion in the form of metabolites.

The major metabolite of medroxyprogesterone acetate is a 6 alpha-methyl-6 beta, 17 alpha, 21-trihydroxy-4-pregnene-3, 20-dione-17-acetate, which is eliminated in the urine. This accounts for approximately 8% of an oral dose, and is found to be excreted as a glucuronide conjugate.

A comparative, single-dose, two-way bioavailability study was performed on two 5 mg medroxyprogesterone acetate tablet formulations, pms-MEDROXYPROGESTERONE 5 mg tablets and Provera[®] 5 mg tablets. The pharmacokinetic data calculated for a single oral dose of 2 X 5 mg tablets (medroxyprogesterone acetate tablet formulations pms-MEDROXYPROGESTERONE versus PROVERA[®]) under fasting conditions are tabulated below:

Pharmacokinetic Indices for Medroxyprogesterone Acetate

	Geometric Mean Arithmetic Mean (C.V.)		
	Medroxyprogesterone (2 x 5 mg)	Provera ^{®**} (2 x 5 mg)	
AUC _T (pg•hr/mL)	5271 5782 (49)	5014 5555 (45)	105
AUC ₀₋₇₂ (pg•hr/mL)	5569 6066 (47)	5345 5887 (44)	104
AUC _I (pg•hr/mL)	6311 7025 (54)	6124 6782 (45)	103
C _{max} (pg/mL)	854 959 (55)	821 943 (62)	104
T _{max} * (hr)	2.9 (1.5)	2.9 (1.7)	---
T _{1/2} * (hr)	14.0 (16)	12.9 (11)	---

*For the T_{max} and T_{1/2} parameters these are the arithmetic means (standard deviation).

**Provera[®] manufactured by The Upjohn Company of Canada.

INDICATIONS AND CLINICAL USE

pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate) is indicated for the following conditions:

1. for hormonal replacement therapy, to oppose the effects of estrogen on the endometrium and significantly reduce the risk of hyperplasia and carcinoma
2. functional menstrual disorders due to hormonal imbalance in non-pregnant women, in the absence of organic pathology
3. adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial carcinoma
4. adjunctive and/or palliative treatment of hormonally-dependent, recurrent metastatic breast cancer in post-menopausal women

CONTRAINDICATIONS

pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate) is contraindicated in patients with any of the following disorders:

- Active hepatic dysfunction or disease, especially the obstructive type
- Personal history of known or suspected estrogen/progestin-dependent neoplasia such as carcinoma of the breast or endometrial cancer, with the exception of cases where pms-MEDROXYPROGESTERONE is used in the adjunctive and/or palliative treatment of such cancers.
- Undiagnosed abnormal genital bleeding
- Undiagnosed urinary tract bleeding
- Known or suspected pregnancy or for use as a pregnancy test (see WARNINGS)
- Active or past history of cerebral apoplexy or arterial thromboembolic disease (eg. Stroke, myocardial infarction, coronary heart disease)
- Classical migraine
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis

- Partial or complete loss of vision due to ophthalmic vascular disease
- Known or suspected hypersensitivity to medroxyprogesterone acetate or any component of the product (see PHARMACEUTICAL INFORMATION)

WARNINGS

See **Boxed Warnings** at the front page.

Liver function tests should be carried out periodically in patients who have or are suspected of having hepatic disease. The physician should watch for the earliest signs of impaired liver function. If these occur or are suspected, treatment should be terminated and the patient's condition re-evaluated.

Cardiovascular Disorders

Available epidemiological data indicate that use of estrogen with or without progestin is associated with an increased risk of stroke, and coronary heart disease. WHI-trial's results concluded that there are more risks than benefits among women using combined Hormone Replacement Therapy (HRT), compared to the group using placebo. In 10,000 women on combined HRT (conjugated equine estrogens/ medroxyprogesterone acetate) over one year period, there were seven more cases of coronary heart disease (37 on combined HRT versus 30 on placebo) and eight more cases of strokes (29 vs. 21).

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763; average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit.

Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.

Breast Cancer

Current epidemiological data indicate that the use of combined HRT is associated with an increased risk of invasive breast cancer. WHI-trial's results concluded that there are more risks than benefits among women using combined HRT (conjugated equine estrogens/medroxyprogesterone acetate), compared to the group using placebo. In 10, 000 women on combined HRT over one year period, there were eight more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).

The WHI study reported that the invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology but were larger (mean[SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group.

The WHI trial also reported that the percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the estrogen plus progestin group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.

It is recommended that estrogens with or without progestins not be given to women with existing breast cancer or those with a previous history of the disease. There is a need for caution in

prescribing estrogens with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy). Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with HRT (as reported in the results of WHI-trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counseling.

Venous Thromboembolism

Recent epidemiological data indicate that use of estrogen with or without progestin is associated with an increased risk of developing venous thromboembolism (VTE). WHI-trial's results concluded that there are more risks than benefits among women using combined HRT (conjugated equine estrogens/ medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over a period of one year, there were eighteen more cases of total blood clots in the lungs and legs (34 on combined HRT versus 16 on placebo).

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic

predisposition) and severe obesity (body mass index >30 kg/m²). The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major elective surgery or posttraumatic surgery, or major trauma (if feasible, estrogens with or without progestins should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization). In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately.

Dementia

Current epidemiological evidence indicates that the use of combined HRT is associated with a significantly increased risk of developing probable dementia. The Women's Health Initiative Memory Study, a clinical substudy of WHI, followed 4532 post-menopausal women age 65 and over and free of dementia at baseline. There was a reported two-fold increase in the relative risk of developing probable dementia after an average follow-up of 4.05 years in the group treated with daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone versus those treated with placebo (hazard ratio [HR] 2.05, 95% confidence interval [CI] 1.21-3.48). This increased risk would result in an additional 23 cases of dementia per 10,000 women per year (45 vs 22 per 10,000 person-years; P = .01).

Additional Warnings

Usage in pregnancy is not advised. Progestational agents should also not be used as a diagnostic test for pregnancy (see CONTRAINDICATIONS). If the patient is exposed to medroxyprogesterone acetate during pregnancy or if she becomes pregnant while taking the drug, she should be apprised of the potential risk to the fetus.

If there is a sudden loss of vision, whether partial or complete, or sudden onset of proptosis, diplopia or migraine, an examination should be carried out. Upon examination, if papilledema or retinal vascular lesions are found, the drug should be discontinued.

Clinical suppression of adrenocortical function has not been observed at low dose levels. However, the high doses of medroxyprogesterone acetate used in the treatment of certain cancers, in some cases, produce Cushingoid symptoms (e.g., 'moon' facies, fluid retention, glucose intolerance, and blood pressure elevation).

Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioral effects through puberty. No adverse effects have been noted.

Anaphylactic and anaphylactoid reactions have occurred at times in people taking medroxyprogesterone acetate.

PRECAUTIONS

- Before pms-MEDROXYPROGESTERONE is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year and should include at least those procedures outlined above. It is important that patients are encouraged to practice frequent self-examination of **the breasts**.

- Abnormal vaginal bleeding due to its prolongation, irregularity or heaviness, occurring during therapy should prompt diagnostic measures like hysteroscopy endometrial biopsy or curettage to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.
- Patients should be advised of the menstrual bleeding patterns expected with the sequential regimen. (see DOSAGE AND ADMINISTRATION).
- Upon sequential administration of pms-MEDROXYPROGESTERONE to women with adequate levels of estrogen (endogenous or exogenous), withdrawal bleeding usually occurs within 7 days after stopping pms-MEDROXYPROGESTERONE. Bleeding that occurs during pms-MEDROXYPROGESTERONE administration indicates a need for a longer duration, or a higher dose of pms-MEDROXYPROGESTERONE (see DOSAGE AND ADMINISTRATION).
- Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.
- If feasible, estrogens with or without progestins should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.
- Women using hormonal replacement therapy (HRT) sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT therapy may have to be discontinued.
- Progestins may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. Treatment should be stopped if there is an increase in epileptic seizures. If, in any of the above mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.
- Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

- A worsening of glucose tolerance and lipid metabolism has been observed in a significant percentage of peri-and post-menopausal patients. A decrease in glucose tolerance has been observed in some patients on progestins. The mechanism of this is obscure. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride levels.
- Women with familial hypertriglyceridemia or porphyria need special surveillance. Lipid lowering measures are recommended additionally, before treatment is started.
- Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under **Laboratory Tests**.
- Patients with a history of mental depression should be carefully monitored while receiving therapy with pms-MEDROXYPROGESTERONE. Some patients may complain of premenstrual like depression while on pms-MEDROXYPROGESTERONE.
- The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.

DRUG INTERACTIONS

Rifampin can increase the metabolism of exogenously administered progestational agents. The extent to which rifampin may alter the metabolism of pms-MEDROXYPROGESTERONE remains to be determined; the possibility of an interaction should be considered.

Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered progestins.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Concomitant administration of aminoglutethimide with medroxyprogesterone acetate (MPA) may significantly reduce the bioavailability of MPA.

A small study in patients with advanced breast cancer studied the influence of MPA given orally in high doses (500 mg twice daily) on the pharmacokinetics of antipyrine (1000 mg dose; N=9), digitoxin (dose unspecified; N=3), and warfarin (0.30 mg/kg dose; N=4). The half-life of antipyrine was decreased, while that of warfarin was increased when MPA was taken concomitantly. Small changes in clearance were noted for antipyrine, digitoxin and warfarin. In the case of warfarin, the minor decrease in clearance that was observed may be clinically important. Coagulation tests should be appropriately monitored.

It was found that some herbal products (e.g. St. John's Wort) which are available as OTC products might effect metabolism, and therefore, efficacy and safety of estrogen/ progestin products.

Red clover isoflavones have affinity for estradiol-alpha and -beta receptors and may act as both agonists and antagonists. Red clover may enhance the estrogenic effects of hormonal contraceptives and may have antiprogestin effects.

Physicians and other health care providers should be aware of other non-prescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

Laboratory Tests

The results of certain endocrine and liver function tests may be affected by progestin-containing products:

- Reduced response to the METOPIRONE test;
- Impaired glucose tolerance

- Reduced serum folate concentration;
- Change in lipoprotein levels
- Gonadotropin levels
- Plasma progesterone levels
- Urinary progesterone levels
- Plasma testosterone levels (in the male)
- Plasma estrogen levels (in the female)
- Plasma cortisol levels

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks. The pathologist should be informed that the patient is receiving HRT therapy when relevant specimens are submitted.

ADVERSE REACTIONS

See Warnings and Precautions regarding potential induction of malignant neoplasma and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combination in general:

- **Gastrointestinal**

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain); bloating; gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

- **Genitourinary**

Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; dysuria; endometrial hyperplasia; pre-menstrual-like

syndrome; reactivation of endometriosis; cystitis; changes in cervical erosion and amount of cervical secretion.

- **Skin**

Chloasma or melasma; which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

- **Endocrine**

Breast swelling and tenderness; increased blood sugar levels; decreased glucose tolerance; sodium retention.

- **Cardiovascular/Hematologic**

Palpitations; isolated cases of thrombophlebitis; thromboembolic disorders; exacerbations of varicose veins; increase in blood pressure (**see Warnings and Precautions**), Coronary thrombosis; altered coagulation tests (**see Laboratory Tests under Precautions**).

- **Central Nervous System**

Aggravation of migraine episodes; headaches; mental depression; nervousness; dizziness; fatigue; irritability; neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis).

- **Ophthalmic**

Visual disturbances; steepening of the corneal curvature; intolerance to contact lenses; neuro-ocular lesions (**see CNS above**)

- **Miscellaneous**

Changes in appetite; changes in body weight; edema; neuritis; change in libido; musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

If adverse symptoms persist, the prescription of HRT should be re-considered.

The following adverse reactions have been associated with the use of pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate):

- **Breast** - tenderness, galactorrhea
- **Reproductive System** - breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, changes in cervical erosion and cervical secretions
- **Central Nervous System** - headache, nervousness, dizziness, depression, insomnia, somnolence, fatigue, premenstrual syndrome-like symptoms
- **Thromboembolic Phenomena** - including thrombophlebitis and pulmonary embolism
- **Skin and Mucous Membranes** - sensitivity reactions ranging from pruritus, urticaria, angioneurotic edema to generalized rash and anaphylaxis; acne, alopecia, hirsutism
- **Gastrointestinal** - abdominal discomfort, nausea, bloating
- **Miscellaneous** - pyrexia, increase in weight, peripheral edema, "moon" facies.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Progestin (norethindrone acetate) over dosage has been characterized by depressed mood, tiredness, acne and hirsutism.

In females, an overdose could cause a period of amenorrhea of a variable length and could be followed by irregular menses for several cycles.

There have been no overdoses reported in males. If overdose were to occur in males however, there would probably be no symptoms.

Doses as high as 1000 mg have been taken for the treatment of endometrial carcinoma without any adverse reaction.

Treatment

There is no specific treatment for overdose with medroxyprogesterone.

DOSAGE AND ADMINISTRATION

1. Hormone Replacement Therapy:

Progestin Challenge Test: Subsequent to the diagnosis of menopause, the progestin challenge test is recommended for amenorrheic women with an intact uterus. pms-MEDROXYPROGESTERONE 10 mg daily should be administered for 10 days.

A negative test is identified by the absence of withdrawal bleeding, and implies the absence of endometrial stimulation due to insufficient estrogen secretion. In these women, hormone replacement therapy consisting of estrogen therapy, and concurrent pms-MEDROXYPROGESTERONE, should be considered.

A positive test is indicated by the presence of withdrawal bleeding which occurs within 7 days after stopping pms-MEDROXYPROGESTERONE treatment. Withdrawal bleeding implies the presence of sufficient endogenous estrogen to stimulate the endometrium. pms-MEDROXYPROGESTERONE therapy should be administered, as above, until withdrawal bleeding no longer occurs. This cessation of withdrawal bleeding indicates the absence of endometrial stimulation due to a decline in estrogen secretion. In these women, hormone replacement therapy consisting of estrogen therapy, and concurrent pms-MEDROXYPROGESTERONE, should be considered.

Sequential Therapy:

Days of the Month																														
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sequential Estrogen - 25 days																														
															Start	pms-MEDROXYPROGESTERONE 5-10 mg/day														
Continuous Estrogen - everyday																														
pms-MEDROXYPROGESTERONE 5-10 mg/day															Stop															

In women with an intact uterus receiving estrogen replacement therapy, pms-MEDROXYPROGESTERONE tablets may be given in a dosage of 5-10 mg daily for 12-14 days. The recommended starting dose for pms-MEDROXYPROGESTERONE should be 10 mg/day, administered for 12-14 days. A dose of 5 mg/day pms-MEDROXYPROGESTERONE for 12-14 days may be appropriate for some women.

Note: The lowest dose of pms-MEDROXYPROGESTERONE required to protect the endometrium from estrogenic-hyperstimulation should be used. A good indicator is the lowest dose of pms-MEDROXYPROGESTERONE that will consistently result in withdrawal bleeding within 7 days after stopping pms-MEDROXYPROGESTERONE treatment. Bleeding that occurs during the pms-MEDROXYPROGESTERONE treatment indicates a need for a longer duration, or higher dose of pms-MEDROXYPROGESTERONE.

2. Functional Menstrual Disorders:

Secondary Amenorrhea: After ruling out pregnancy, pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate) can be used in doses ranging from 5-10 mg daily depending on the amount of endometrial stimulation required. The dose should be given daily for 12-14 days every month.

Note: In patients with an underdeveloped endometria, standard estrogen therapy should be administered in combination with pms-MEDROXYPROGESTERONE. Withdrawal bleeding normally occurs within 3 days of commencement of combination therapy of estrogen and pms-MEDROXYPROGESTERONE.

Dysfunctional Uterine Bleeding: pms-MEDROXYPROGESTERONE can be administered in doses ranging from 5-10 mg for 10-14 days commencing on the assumed or calculated 12-16th day of the cycle. This regimen should be repeated for 2 subsequent cycles or longer if necessary.

When bleeding is caused by a lack of both ovarian hormones, as evidenced by an under-developed proliferative endometrium, estrogens should be given in combination with medroxyprogesterone acetate. If this controls the bleeding satisfactorily, treatment should be maintained for at least two subsequent cycles.

If dysfunctional uterine bleeding is not controlled by hormone therapy, appropriate diagnostic measures should be undertaken to rule out uterine pathology.

3. Endometrial Cancer:

200 - 400 mg/day is the usual dose. It is suggested that if neither subjective nor objective improvement is noted within 2 to 3 months, therapy should be discontinued. Where improvement is noted and the disease process appears to be stabilized, it may be possible to maintain this improvement with a 200 mg/day dose.

pms-MEDROXYPROGESTERONE should only be used as adjunctive and palliative treatment in advanced, inoperable cases including those with recurrent metastatic disease, and is not recommended as primary therapy.

Note: Response to hormonal therapy for endometrial or breast cancer may not be evident until 8 to 10 weeks of therapy. Rapid progression of disease at any time during therapy should result in termination of treatment with pms-MEDROXYPROGESTERONE.

4. Breast Cancer:

The recommended dose is 400 mg daily, given in divided doses. The patient should be continued on therapy as long as she is responding to treatment. Although doses of up to 2400 mg daily have been reported, controlled studies using 800 mg daily did not demonstrate any appreciable increase in response rates compared to the 400 mg daily dose.

pms-MEDROXYPROGESTERONE should only be used as adjunctive and palliative treatment in advanced, inoperable cases including those with recurrent metastatic disease, and is not recommended as primary therapy.

Note: Response to hormonal therapy for endometrial or breast cancer may not be evident until 8 to 10 weeks of therapy. Rapid progression of disease at any time during therapy should result in termination of treatment with pms-MEDROXYPROGESTERONE.

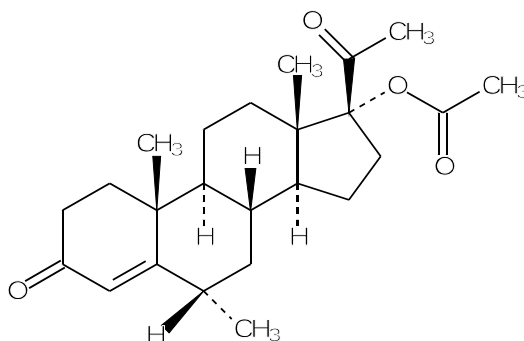
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Medroxyprogesterone Acetate

Chemical Name: 17-Hydroxy-6 α -methylpregn-4-ene-3,20-dione acetate.

Structural Formula:



Molecular Formula: C₂₄H₃₄O₄

Molecular Weight: 386.53

Description: White to off-white odorless crystalline powder, stable in air, with a melting point of 205°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Non-medicinal Ingredients: pms-MEDROXYPROGESTERONE tablets contain: calcium stearate, lactose, light mineral oil, sorbic acid, starch (corn), sucrose, talc. Colouring Agents: 2.5 mg tablets: FD & C Yellow #6 Lake; 5 mg tablets FD & C Blue #2 Lake.

Stability and Storage Recommendations: Bottles of medroxyprogesterone acetate tablets should be stored in tight, light-resistant containers at a temperature between 15°–30°C.

AVAILABILITY OF DOSAGE FORMS

pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate) 2.5 mg tablets are peach coloured, round, scored and engraved with 'P2.5' on one side and contain 2.5 mg of medroxyprogesterone acetate. They are available in bottles of 100 and 500.

pms-MEDROXYPROGESTERONE 5 mg tablets are blue, round, engraved with 'P5' and contain 5 mg of medroxyprogesterone acetate. They are available in bottles of 100 and 500.

pms-MEDROXYPROGESTERONE 10 mg tablets are white, round, engraved with 'P10' and contain 10 mg of medroxyprogesterone acetate. They are available in bottles of 100 and 500.

PATIENT INFORMATION

^{Pr}pms-MEDROXYPROGESTERONE

(Medroxyprogesterone acetate Tablets USP)

2.5mg, 5 mg and 10 mg

Please read this PATIENT INFORMATION carefully before you start using pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate) and each time you refill your prescription. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. If you have any questions or concerns, you should speak with your doctor or your pharmacist.

Warning

The Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (heart attack), stroke, invasive breast cancer, pulmonary emboli (blood clots in the lungs) and deep venous thrombosis (blood clots in the leg veins) in postmenopausal women receiving treatment with combined conjugated equine estrogens and medroxyprogesterone acetate compared to women receiving placebo (sugar pill).

In light of these findings, the following should be highly considered:

- Estrogens with or without progestins **should not** be prescribed for the prevention of heart disease or stroke
- Use of estrogens with or without progestins may increase your risk of developing invasive breast cancer, stroke, heart attack and blood clots in both legs and lungs
- Treatment with estrogens with or without progestins, should be at the **lowest effective dose** and for the **shortest period of time** possible.

INTRODUCTION

What is pms-MEDROXYPROGESTERONE?

pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate) is a progestin (a female hormone) derived from a natural source (soybeans). pms-MEDROXYPROGESTERONE also contains some other non-medicinal ingredients that you should be aware of (see **PHARMACEUTICAL INFORMATION**).

pms-MEDROXYPROGESTERONE is available in tablets containing 2.5 mg and 5.0 mg and 10 mg of medroxyprogesterone acetate and is approved for use in a number of different situations (see **INDICATIONS**). The dose of pms-MEDROXYPROGESTERONE depends on its reason for use (see **HOW TO USE**).

pms-MEDROXYPROGESTERONE should be used only under a doctor's supervision. You and your doctor should talk regularly about how long you will need treatment with pms-MEDROXYPROGESTERONE.

Your first follow-up visit with your doctor should be within 3-6 months after starting treatment. Thereafter, you should see your doctor at least once a year while taking pms-MEDROXYPROGESTERONE to identify possible adverse events associated with its use. Your visit may include a blood pressure check, a breast exam and a Pap smear and pelvic exam. Your doctor may suggest scheduling regular mammograms (breast x-rays) and may recommend some blood tests.

INDICATIONS

pms-MEDROXYPROGESTERONE is approved for use in the following situations:

1) For hormone replacement therapy: pms-MEDROXYPROGESTERONE is used in addition to estrogen to counter the estrogen effect on the endometrium (lining of the uterus) to reduce the risk of endometrial hyperplasia (overgrowth of the lining of the uterus) and endometrial cancer (cancer of the lining of the uterus).

2) In non-pregnant women, for the treatment of certain menstrual disorders related to hormonal imbalance.

3) As part of treatment for recurrent and/or metastatic endometria carcinoma (cancer of the lining of the uterus)

4) As part of treatment of hormonally-dependent, recurrent metastatic breast cancer in post-menopausal women.

RESTRICTIONS ON USE

WHO SHOULDN'T TAKE pms-MEDROXYPROGESTERONE

You should not take pms-MEDROXYPROGESTERONE if you:

- have active liver disease
- have noticed any breast lumps or breast changes that have not yet been diagnosed
- have experienced undiagnosed or abnormal genital bleeding
- have experienced undiagnosed or abnormal urinary tract bleeding
- have a history of heart attack, heart disease or stroke
- experience migraine headaches
- have a personal history of blood clots or active thrombophlebitis (inflammation of the veins)
- have had partial or complete loss of vision due to blood vessel disease of the eye

- are pregnant or think you may be pregnant (pms-MEDROXYPROGESTERONE should not be used as a pregnancy test)
- have had an allergic or unusual reaction to pms-MEDROXYPROGESTERONE or to any of its ingredients (see **PHARMACEUTICAL INFORMATION**).

WARNINGS AND PRECAUTIONS

See the **Boxed Warnings** at the front page.

Cardiovascular Disorders

The use of combined estrogen and progestin therapy by post-menopausal women has been associated with an increased risk of heart attack and stroke.

The use of estrogens with or without progestins should not be used for the prevention of heart disease or stroke.

Breast Cancer

The use of combined estrogen and progestin therapy by post-menopausal women has been associated with an increased risk of invasive breast cancer.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer. In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting hormone replacement therapy (HRT).

Women should have a mammogram (breast x-ray) before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women.

Venous Thromboembolism

The use of combined estrogen and progestin therapy by post-menopausal women has been associated with an increased risk of blood clots in the lungs and legs. This risk also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and with major surgery.

Dementia

Current studies indicate that the use of combined estrogen and progestin in women age 65 and over may increase the risk of developing probable dementia (loss of memory and intellectual function).

Additional Warnings

Pregnancy

pms-MEDROXYPROGESTERONE should not be used in pregnancy (see **RESTRICTIONS ON USE**). Stop taking pms-MEDROXYPROGESTERONE and inform your doctor as soon as possible if you become pregnant while taking pms-MEDROXYPROGESTERONE.

Breast Feeding

You should discuss the risks and benefits of pms-MEDROXYPROGESTERONE use and breast feeding with your doctor.

Other

The high doses of medroxyprogesterone acetate used in the treatment of certain cancers can cause adverse side effects such as "moon" face (roundness of the face), fluid retention, glucose intolerance and increase in blood pressure.

Before using this medication

To help your doctor decide if you should use pms-MEDROXYPROGESTERONE and what precautions should be taken during its use tell your doctor if you:

- have a history of liver disease or jaundice (yellowing of the eyes and/or skin)
- have a personal or family history of known or suspected breast cancer or a personal history of endometrial cancer (cancer of the lining of the uterus)
- have noticed any breast lumps or breast changes
- have experienced any undiagnosed or abnormal vaginal bleeding
- have experienced any undiagnosed or abnormal urinary tract bleeding
- have history of heart attack, heart disease or stroke
- experience migraine headaches
- have a personal or family history of blood clots (including blood clots in the legs or lungs), or a personal history of active thrombophlebitis (inflammation of veins)
- have had a partial or complete loss of vision due to blood vessel disease of the eye
- are pregnant or may be pregnant (**Do not use this drug to test if you are pregnant**)
- have experienced an allergic or unusual reaction to pms-MEDROXYPROGESTERONE, to any of its ingredients (see **PHARMACEUTICAL INFORMATION**), or to any other medications or substances.

- are breast feeding or intend to breast feed
- smoke
- have a history of kidney disease, asthma or epilepsy
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- are diabetic or have been told you are at risk of developing diabetes
- have been diagnosed with porphyria
- have a history of high cholesterol or high triglycerides
- have a history of depression
- know you are going to have major surgery in the near future. Periods of prolonged immobilization, such as after surgery, may be associated with an increased risk of blood clots.
- If you are taking any other prescription medications, over-the-counter medications or herbal products.

ADVERSE EFFECTS

See also **WARNINGS AND PRECAUTIONS**

The following lists some of the possible unwanted effects associated with the use of pms-MEDROXYPROGESTERONE, either by itself or in combination with estrogen as part of hormone replacement therapy. Check with your doctor as soon as possible if you experience any of these events:

Gastrointestinal

Nausea, vomiting, abdominal discomfort, (cramps, pressure, pain); bloating, gallbladder disorder; impaired liver function [possibly indicated by jaundice (yellow eyes)].

Genitourinary

Genital bleeding; spotting; changes in menstrual flow; painful periods; vaginal itching/discharge; pain during sexual intercourse; pain or discomfort with urination; endometrial hyperplasia (overgrowth of the lining of the uterus); pre-menstrual-like syndrome, cervical secretions.

Skin

Changes to the face pigmentation; loss of scalp hair; hirsutism (excessive hair growth); acne; skin reactions and rashes.

Endocrine

Breast swelling and tenderness; increased blood sugar levels; decreased glucose tolerance; sodium retention.

Cardiovascular/hematologic

Palpitations; blood clots; thrombophlebitis (inflammation of veins); worsening of varicose veins; increase in blood pressure.

Central Nervous System

Aggravation of migraine episodes; headaches; mental depression; nervousness; dizziness; fatigue; irritability.

Ophthalmic

Visual disturbances; intolerance to contact lenses; lesions affecting the blood vessels or nerves of the eye.

Miscellaneous

Changes in appetite; changes in body weight; swelling; change in libido; musculoskeletal pain including leg pain.

Note: These are not all of the possible side effects of pms-MEDROXYPROGESTERONE, either by itself or in combination with estrogen as part of hormone replacement therapy. You should contact your doctor or pharmacist if you experience any side effects or have any questions.

The following adverse reactions have been associated with the use of pms-MEDROXYPROGESTERONE (medroxyprogesterone acetate):

- breast tenderness, unexpected or increased flow of milk from the breasts or breast discharge
- vaginal bleeding, changes in menstrual flow, vaginal discharge
- headache, nervousness, dizziness, depression, insomnia (inability to sleep), sleepiness, tiredness
- premenstrual syndrome-like symptoms
- blood clots in the legs or lungs

- allergic reaction, possibly including itching, hives, generalized rash, swelling of the face, lips, tongue and/or throat
- acne
- hair loss, increased hair growth
- stomach discomfort, nausea, bloating
- fever
- weight gain
- swelling of the hands, feet or ankles

HOW TO USE

Take pms-MEDROXYPROGESTERONE only as directed by your doctor. Do not take more of it and do not take it for a longer time than your doctor ordered. To do so may increase the chance of side effects. Try to take pms-MEDROXYPROGESTERONE at the same time each day to reduce the possibility of side effects and to allow it to work better. pms-MEDROXYPROGESTERONE should be taken with food to help prevent nausea that might occur during first few weeks of treatment.

pms-MEDROXYPROGESTERONE is often given together with certain other medicines. Some medications can interfere with the action of pms-MEDROXYPROGESTERONE and pms-MEDROXYPROGESTERONE can interfere with the action of other medications. When you are taking pms-MEDROXYPROGESTERONE it is important to let your doctor know if you are taking any other medications, including prescription medications, over-the-counter medications,

vitamins and herbal products. If you are using a combination of medicines, make sure that you take each one at the proper time and follow your doctor's instructions.

The dose of pms-MEDROXYPROGESTERONE will be different for different patients and condition being treated. Follow your doctor's instructions.

The following information includes only the recommended doses of pms-MEDROXYPROGESTERONE. If your dose is different, do not change it unless your doctor tells you to do so.

The usual doses of pms-MEDROXYPROGESTERONE are:

1. Hormone Replacement Therapy:

When used as a component of hormone replacement therapy in women who have not had a hysterectomy (surgical removal of the uterus), pms-MEDROXYPROGESTERONE tablets may be taken in doses ranging from 5-10 mg daily for a minimum of 12 to 14 days per cycle, as directed by your doctor.

Days of the Month																															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Sequential Estrogen - 25 days																															
													Start	pms-MEDROXYPROGESTERONE 5-10 mg/day																	
Continuous Estrogen - everyday																															
pms-MEDROXYPROGESTERONE 5-10 mg/day													Stop																		

2. Functional Menstrual Disorders

a) Secondary Amenorrhea (abnormal discontinuation of menstrual periods):

For secondary amenorrhea, after ruling out pregnancy, pms-

MEDROXYPROGESTERONE tablets may be taken in doses ranging from 5 to 10 mg daily for 12 to 14 days per month as recommended by your doctor. If your doctor determines that you have a poorly developed uterine lining, your doctor may also suggest that you take estrogen therapy in addition to pms-MEDROXYPROGESTERONE.

b) Dysfunctional Uterine Bleeding (abnormal uterine bleeding):

For dysfunctional uterine bleeding, pms-MEDROXYPROGESTERONE may be taken in doses ranging from 5 to 10 mg daily for 10-14 days beginning on the assumed or calculated 12th to 16th day of your cycle.

When bleeding is due to a deficiency of both estrogen and progestin as determined by your doctor, estrogen therapy should be taken in addition to pms-MEDROXYPROGESTERONE. If bleeding is controlled satisfactorily, two subsequent cycles of treatment should be given. If dysfunctional uterine bleeding is not controlled by hormone therapy, appropriate tests should be done to rule out the possibility of uterine disease.

3. Recurrent and/or metastatic endometrial carcinoma (cancer of the lining of the uterus):

As prescribed by your doctor

4. Hormonally-dependent, recurrent metastatic breast cancer in post-menopausal women:

As prescribed by your doctor

Missed Dose

If you miss a dose of pms-MEDROXYPROGESTERONE, take the missed dose as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

Vaginal Bleeding

Before starting pms-MEDROXYPROGESTERONE, discuss with your doctor what to expect with respect to vaginal bleeding. Contact your doctor if you experience any unusual or unexpected vaginal bleeding.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

In female patients, overdose may result in abnormal discontinuation of menstrual periods followed by irregular menstrual periods for several cycles. Overdose with another progestin (norethindrone acetate) has been characterized by depressed mood, tiredness, acne and hirsutism (excessive hair growth).

Treatment

In the case of accidental overdose, contact your doctor, your nearest hospital emergency department and/or your local Poison Control Centre immediately.

PHARMACEUTICAL INFORMATION

The medicinal ingredient in pms-MEDROXYPROGESTERONE tablets is Medroxyprogesterone Acetate.

Non-medicinal Ingredients: pms-MEDROXYPROGESTERONE tablets contain: calcium stearate, lactose, light mineral oil, sorbic acid, starch (corn), sucrose, talc. Colouring Agents: 2.5 mg tablets: FD & C Yellow #6 Lake; 5 mg tablets FD & C Blue #2 Lake.

STORAGE

pms-MEDROXYPROGESTERONE tablets should be stored in tight, light-resistant containers at a temperature between 15°–30°C. The medication should be kept out of the reach of children.

PHARMACOLOGY

Animal Studies

Medroxyprogesterone acetate causes responses in laboratory animals similar to those produced by progesterone. It is more potent than progesterone. Medroxyprogesterone acetate causes glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It lacks any androgenic and estrogenic activity. In certain animal tests, it demonstrates some adrenal corticoid-like activity and in dogs, it causes a rise in serum growth hormone levels.

Human Studies

(See ACTIONS AND CLINICAL PHARMACOLOGY)

TOXICOLOGY

ANIMAL STUDIES

Acute Toxicity : The oral LD₅₀ of medroxyprogesterone acetate was found to be greater than 10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Sub-Acute and Chronic Toxicity

Medroxyprogesterone acetate was administered orally to rats and mice at doses of 334 mg/kg/day and to dogs at doses of 167 mg/kg/day for 30 days was found to be non-toxic.

Medroxyprogesterone was given orally to dogs and rats at doses of 3, 10 and 30 mg/kg/day for 6 months. The drug was well-tolerated without toxic effects at these levels but is expected to have hormonal effects at higher doses.

Reproduction and Fertility

Medroxyprogesterone was administered orally at doses of 1, 10 and 50 mg/kg/day to pregnant beagle dogs. Clitoral hypertrophy was observed in the female pups of the mothers in the high dose group. There were no abnormalities in the male pups. Subsequent analysis of the reproductive abilities of the female dogs from the litters of the treated females found no impairment in fertility potential.

Animal studies have not confirmed any impairment of fertility in first or second generation studies.

In rats, medroxyprogesterone acetate may have some effect on genital systems, but standard teratologic techniques have shown no effects on non-genital systems.

The relevance of any of these findings with respect to humans has not been established.

Carcinogenicity

Long-term toxicity studies in the monkey, dog and rat given parenteral medroxyprogesterone acetate have revealed the following:

Beagle dogs given 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules that were larger, more numerous, and more persistent than the occasional nodules found in control animals. Also, two high dose animals developed breast malignancies.

The Food and Drug Administration (United States), the Committee on Safety of Medicines (United Kingdom), and 3 International panels of experts have concluded that the Beagle bitch is not an appropriate model for mammary carcinogenicity testing of progesterone derivatives such as medroxyprogesterone acetate.

Because of differences between the Beagle bitch and the human female with regard to sensitivity and metabolism of progestins, positive carcinogenicity studies in the Beagle bitch can no longer be considered indicative of a significant hazard to women.

- No uterine malignancies were found in monkeys receiving placebo, 3mg/kg, or 30mg/kg every 90 days for 10 years. However, two monkeys receiving 150 mg/kg every 90 days for 10 years developed endometrial carcinoma. One was treated for 111 months and the other for 125 months of the 130 month study. The lesions were remarkably similar in cell morphology to epithelial plaques which occur in monkeys but not in humans. Electron microscopic studies confirmed that the neoplasms were malignant, epithelial (not mesenchymal), and thus of a type not stimulated by progestins in women. Therefore, it was concluded that the occurrence of these lesions, regardless of the cause, does not indicate medroxyprogesterone acetate is carcinogenic in women.

In the same study, mammary nodules were found in three of the monkeys in the 30mg/kg group. The lesions showed no signs of malignancy. Because these lesions were both non-progressive and non-invasive, and because many lesions of this type are known to appear and then regress, it was concluded that the occurrence of this non-malignant mammary lesion in 3 treated monkeys poses no potential risk of breast cancer in women.

Mutagenicity

The micronucleus test and the salmonella/microsome test (Ames Assay) have not indicated that medroxyprogesterone is mutagenic.

The significance of these findings with respect to clinical use is unknown.

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