PRODUCT MONOGRAPH

NU-MEDROXY

Medroxyprogesterone Acetate Tablets USP

2.5 and 5 mg

PROGESTIN

Nu-Pharm Inc.
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Richmond Hill ON
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DATE OF PREPARATION:
April 20, 2004

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PRODUCT MONOGRAPH

NU-MEDROXY

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THERAPEUTIC 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**.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible.

ACTIONS AND CLINICAL PHARMACOLOGY

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), medroxyprogesterone acetate transforms a proliferative endometrium into a secretory endometrium.

Pharmacokinetics

Medroxyprogesterone acetate has an apparent half-life of about 30 hours. It 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 only metabolite of medroxyprogesterone acetate that has been isolated and unequivocally identified is 6α-methyl-6β,17α,21-trihydroxy-4-pregnene-3,20-dione-17-acetate, and appears to be the primary urinary metabolite. This metabolite accounts for approximately 8% of an oral dose, and is excreted as a glucuronide conjugate.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of medroxyprogesterone was measured and compared following oral administration 8 x 2.5 mg of NU-MEDROXY Tablets or Provera® Tablets. The results from measured data are summarized as follows:

Fasting Study: Summary Table of the Comparative Bioavailability Data Medroxyprogesterone (Dose: 8 x 2.5 mg) From Measured Data			
Parameter	**Geometric Mean Arithmetic Mean (CV%)**		**Ratio of Geometric Means (%)** (CI)**
	NU-MEDROXY 2.5 mg Tablets	**Provera† 2.5 mg Tablets**	
AUC_T (pg·hr/mL)	8913.2 11030.5 (70.6)	9926.1 11868.5 (67.5)	89.8 (80.4 - 101.3)
AUC_I (pg·hr/mL)	10020.0 12431.5 (69.9)	11046.3 13414.4 (69.4)	90.7 (83.1 - 103.9)
C_{max} (pg/mL)	1693.48 2045.14 (60.6)	1895.51 2267.95 (63.4)	89.3
T_{max} (hr)*	2.49 (53.1)	2.28 (49.8)	--
$t_{1/2}$ (hr)*	10.97 (62.2)	11.61 (59.3)	--

*Arithmetic means (CV%); **Based on the least squares estimate.
†Provera® is manufactured by Pharmacia & Upjohn Inc., and was purchased in Canada.

INDICATIONS AND CLINICAL USE

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.

CONTRAINDICATIONS

Medroxyprogesterone acetate is contraindicated in patients with any of the following disorders:

1) Active hepatic dysfunction or disease, especially of the obstructive type;

2) Personal history of known or suspected estrogen/progestin-dependent neoplasia such as carcinoma of the breast or endometrial cancer;
3) Undiagnosed breast pathology;
4) Undiagnosed abnormal genital bleeding;
5) Undiagnosed urinary tract bleeding;
6) Known or suspected pregnancy or for use as a pregnancy test (See WARNINGS);
7) Active or past history of cerebral apoplexy or arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease);
8) Classical migraine;
9) Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis;
10) Partial or complete loss of vision due to ophthalmic vascular disease;
11) Known or suspected hypersensitivity to medroxyprogesterone acetate or any component of the product (see PHARMACEUTICAL INFORMATION).

WARNINGS

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

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, last age at first full term pregnancy and at menopause should also 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 counselling.

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/m^2). 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 the 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=0.01).

Additional Warnings

Liver function tests should be performed periodically in patients who have or are suspected of having hepatic disease. The physician should be alert to the earliest manifestations of impaired liver function. Should these occur or be suspected, the drug should be discontinued and the patient's status re-evaluated.

Usage in pregnancy is not recommended. Progestational agents are also not recommended 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.

Patients who develop visual disturbances (including sudden partial or complete loss of vision or diplopia), proptosis or migraine should discontinue medication and symptoms should be appropriately investigated. 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 may, 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 behavioural effects through puberty. No adverse effects have been noted.

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with medroxyprogesterone acetate.

PRECAUTIONS

Before NU-MEDROXY 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.

This drug 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.

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 to be expected with the sequential regimen. Upon sequential administration of medroxyprogesterone acetate to women with adequate levels of estrogen (endogenous or exogenous), withdrawal bleeding usually occurs within 7 days after stopping medroxyprogesterone acetate. Bleeding that occurs during medroxyprogesterone acetate administration indicates a need for a longer duration, or a higher dose of medroxyprogesterone acetate (see DOSAGE AND ADMINISTRATION).

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of conscious 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.

Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

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.

Patients who have a history of mental depression should be carefully monitored while receiving therapy with medroxyprogesterone acetate. Some patients may complain of premenstrual like depression while on medroxyprogesterone acetate.

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 blood 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.**

The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.

DRUG INTERACTIONS

Aminoglutethimide administered concomitantly with medroxyprogesterone acetate may significantly depress the bioavailability of medroxyprogesterone acetate.

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

In one published study, high doses of medroxyprogesterone acetate were shown to have an effect on the disposition of antipyrine, warfarin, and digitoxin in patients with advanced breast cancer. When medroxyprogesterone acetate 500 mg twice daily was administered concomitantly with antipyrine 1000 mg, warfarin 0.3 mg/kg, or an unspecified dose of digitoxin, there was a decrease in the clearance of warfarin and digitoxin and an increase in the clearance of antipyrine. The half-lives were shown to decrease for antipyrine and increase for warfarin. The decrease observed in warfarin clearance may be of clinical importance.

Anticonvulsants such as carbamazepine and phenytoin as well as barbiturates (e.g. phenobarbital) can increase the capacity of sex hormone-binding globulin (SHBG) to bind

progestogens, and therefore may reduce the free concentrations of progestogens in the plasma. These drugs also induce hepatic enzymes and accelerate the rate of metabolism of estrogen and progestogens. There have been reports of drug interactions between anticonvulsants and combined hormone contraceptives that contain ethinylestrodiol and levonorgestrel or norethisterone, however, there is no evidence that demonstrates a drug interaction between anticonvulsants and medroxyprogesterone acetate. In theory, hepatic microsomal enzyme-inducing anticonvulsants may reduce the efficacy of medoxyprogesterone acetate and therefore as a precautionary measure medroxyprogesterone acetate may need to be monitored for reductions in clinical effect.

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

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

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 following laboratory tests may be affected by the use of medroxyprogesterone acetate.

a) Gonadotropin levels
b) Plasma progesterone levels
c) Urinary pregnanediol levels

d) Plasma testosterone levels (in the male)
e) Plasma estrogen levels (in the female)
f) Plasma cortisol levels
g) Glucose tolerance test
h) Metyrapone test
i) Lipoprotein 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 progestin therapy when relevant specimens are submitted.

ADVERSE REACTIONS

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

The following adverse reactions have been associated with the use of 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.

If adverse symptoms persist, the prescription of NU-MEDROXY should be reconsidered.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

In female patients, overdosage may result in a period of amenorrhea of a variable length and may be followed by irregular menses for several cycles.

Doses as high as 1000 mg of medroxyprogesterone acetate for the therapy of endometrial carcinoma have been used without adverse effect.

No cases of overdosage in male patients have been reported. However, such overdosage, if it were to occur, would not likely result in any particular symptomatology.

There is no known therapy for overdosage of medroxyprogesterone.

DOSAGE AND ADMINISTRATION

1) HORMONE REPLACEMENT THERAPY

a) Progestin Challenge Test

Subsequent to the diagnosis of menopause, the progestin challenge test is recommended for amenorrheic women with an intact uterus. Medroxyprogesterone acetate 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 medroxyprogesterone acetate, should be considered.

A positive test is indicated by the presence of withdrawal bleeding which occurs within 7 days after stopping medroxyprogesterone acetate treatment. Withdrawal bleeding implies the presence of sufficient endogenous estrogen to stimulate the endometrium. Medroxyprogesterone acetate 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 medroxyprogesterone acetate, should be considered.

b) Sequential Therapy

<table>
<tr><th colspan="4">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</th></tr>
<tr><td colspan="3">Sequential Estrogen - 25 days</td><td></td></tr>
<tr><td></td><td>Start</td><td>Medroxyprogesterone Acetate Tablets 5 - 10 mg/day</td><td></td></tr>
<tr><td colspan="4">Continuous Estrogen - everyday</td></tr>
<tr><td>Medroxyprogesterone Acetate Tablets 5 - 10 mg/day</td><td>Stop</td><td colspan="2"></td></tr>
</table>

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

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

2) FUNCTIONAL MENSTRUAL DISORDERS

a) Secondary Amenorrhea

After ruling out pregnancy, medroxyprogesterone acetate may be administered in doses ranging from 5 - 10 mg daily depending upon the degree of progestational effect desired. The dose should be given daily for 12 - 14 days every month.

Note: In patients with poorly developed endometria, conventional estrogen therapy should be given in conjunction with medroxyprogesterone acetate.

b) Dysfunctional Uterine Bleeding

In dysfunctional uterine bleeding, medroxyprogesterone acetate may be given in doses ranging from 5 - 10 mg/day, for 10 - 14 days, beginning 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 due to a deficiency of both ovarian hormones, as indicated by a poorly developed proliferative endometrium, conventional estrogen therapy should be given in conjunction with medroxyprogesterone acetate. If bleeding is controlled satisfactorily, at least two subsequent cycles of treatment should be given.

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

PHARMACEUTICAL INFORMATION

Drug Substance

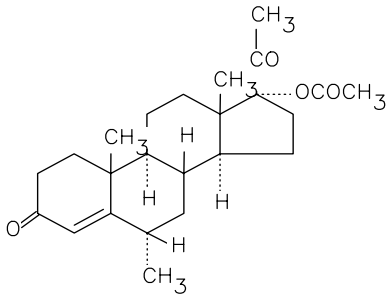
Proper Name: Medroxyprogesterone acetate

Chemical Names:

1) Pregn-4-ene-3,20-dione,17-(acetyloxy)-6-methyl-,(6α)-;

2) 17-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate

Structural Formula:



Molecular Formula: $C_{24}H_{34}O_4$

Molecular Weight: 386.53

Description: Medroxyprogesterone acetate is a white to off-white, odourless crystalline powder, stable in air, melting between 205 and 210°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.

Composition

In addition to medroxyprogesterone acetate, each tablet contains the following non-medicinal ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, sodium lauryl sulfate and colloidal silicon dioxide. The 2.5 mg tablet also contains the colouring agents D&C yellow #10 and FD&C yellow #6. The 5 mg tablet also contains the colouring agent FD&C blue #2.

Stability and Storage Recommendations

Store at room temperature (15 - 30°C).

AVAILABILITY OF DOSAGE FORMS

NU-MEDROXY 2.5 mg: each round, pink orange, biconvex tablet scored and engraved "MED" over "2.5" on one side and “APO” on the other, contains 2.5 mg medroxyprogesterone acetate. Available in bottles of 100.

NU-MEDROXY 5 mg**:** each round, blue, biconvex tablet scored and engraved "MED" over "5" on one side and “APO” on the other, contains 5 mg medroxyprogesterone acetate. Available in bottles of 100.

INFORMATION FOR THE PATIENT

Please read this INFORMATION FOR THE PATIENT before you start using NU-MEDROXY (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 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 estrogen and progestin therapy.

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.

What is NU-MEDROXY?

NU-MEDROXY (medroxyprogesterone acetate) is a progestin, which is a female hormone. NU-MEDROXY also contains some other non-medicinal ingredients that you should be aware of (see **PHARMACEUTICAL INFORMATION**).

Progestins oppose the unwanted action of estrogen (another female hormone) on the lining of the uterus (womb). When used without a progestin, estrogen can cause a condition called endometrial hyperplasia (overgrowth of the lining of the uterus). This overgrowth of the lining of

the uterus can lead to abnormalities of menstrual function as well as development of endometrial cancer (cancer of the uterus).

NU-MEDROXY comes as 2.5 mg and 5.0 mg tablets and should be taken only as directed by your doctor (see **HOW TO USE NU-MEDROXY**).

NU-MEDROXY should be used only under a doctor's supervision.

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 NU-MEDROXY 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 – NU-MEDROXY is approved for use in the following situations:

1) For hormone replacement therapy: NU-MEDROXY is used in addition to estrogen to oppose the estrogen effect on the endometrium (lining of the uterus), in order to reduce the risk of endometrial hyperplasia (abnormal growth 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.

RESTRICTIONS ON USE: WHO SHOULDN'T TAKE NU-MEDROXY

You should not take NU-MEDROXY if you:

- have active liver disease
- have a personal history of breast cancer or endometrial cancer (cancer of the lining of the uterus)
- 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 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 (NU-MEDROXY should not be used as a pregnancy test)
- have had an allergic or unusual reaction to NU-MEDROXY 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 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.

Your doctor may recommend that you temporarily discontinue taking estrogen therapy with or without progestin therapy in advance of expected hospitalizations or surgery. If possible, estrogen therapy with or without progestin therapy should be discontinued at least 4 weeks before 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).

Before using this medication

In deciding to use a medicine, the risks of taking the medicine must be weighed against the benefits it will provide. This is something you should discuss with your doctor. You should also regularly discuss with your doctor how long you will need treatment with NU-MEDROXY.

Before taking NU-MEDROXY, 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 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 NU-MEDROXY, 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 (a disease of blood pigment)

- have a history of high cholesterol or high triglycerides (a chemical form of fat found in the blood)

- 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.

- are taking any other prescription medications, over-the-counter medications or herbal products

ADVERSE EFFECTS

See **WARNINGS AND PRECAUTIONS.**

Along with its needed effects, NU-MEDROXY may cause some unwanted effects. Some side effects will have signs or symptoms that you can see or feel. Your doctor will watch for others by doing certain tests.

Also, because of the way this medicine acts on the body, there is a chance that it might cause other unwanted effects that may not occur until months or years after the medicine is used. **It is therefore very important that you take this drug under the supervision of your physician and have regular follow-up exams at least once a year, to possibly identify any adverse events associated with long-term treatment.**

Drugs containing medroxyprogesterone acetate (the active ingredient of NU-MEDROXY) have been reported to increase the risk of stroke, coronary heart disease, breast cancer, venous

thromboembolism (blood clot in one of the deep veins of the body), and dementia (in post-menopausal women). **You should review the technique for breast self-examination with your doctor and practice frequent self-examinations of the breasts.**

If you develop visual disturbances (including sudden partial or complete loss of vision or double vision), or migraine headaches while taking this medication, you should contact your doctor immediately. The high doses of medroxyprogesterone acetate used in the treatment of certain cancers, can cause adverse effects such as “moon” face (rounding out of the face), fluid retention, glucose (sugar) intolerance and blood pressure elevation. Discuss these possible effects with your doctor.

Check with your doctor or pharmacist as soon as possible if any of the following undesirable events occur:

- Increased blood pressure
- Breast tenderness
- Unexpected or increased flow of breast milk or breast discharge
- Vaginal bleeding
- Changes in menstrual flow
- Vaginal discharge
- Headaches
- Nervousness
- Dizziness

- Depression
- Inability to sleep (insomnia)
- Sleepiness
- Tiredness
- Premenstrual syndrome-like symptoms
- Pain, swelling or redness of the calf or leg which may indicate a blood clot
- Chest pain or shortness of breath which may indicate a blood clot
- Itching
- Generalized rash
- Acne
- Hair loss
- Abnormal hairiness
- Abdominal discomfort
- Nausea
- Bloating
- Fever
- Weight gain
- Swelling (possibly seen in the ankles)

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

STOP TAKING NU-MEDROXY and contact your doctor immediately in any of the following situations:

- **If you develop difficulty in breathing with or without swelling of the face, lips, tongue and/or throat.**

- **If you develop swelling of the face, lips tongue and/or throat which may cause difficulty swallowing**

- **If you develop swelling of the hands, feet or ankles**

- **If you develop 'nettle rash' or 'hives' (urticaria)**

If you need any further information ask your doctor or pharmacist.

HOW TO USE NU-MEDROXY

Use this medication only as directed by your doctor. Do not use more or less of it and do not use it more often than you doctor ordered. Taking too much may increase the chance of side effects, while taking too little may not improve your condition.

NU-MEDROXY is supplied as 2.5 mg and 5 mg tablets to be taken by mouth.

NU-MEDROXY is approved for use in hormone replacement therapy and for treating functional menstrual disorders in non-pregnant women.

1. HORMONE REPLACEMENT THERAPY:

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

2. FUNCTIONAL MENSTRUAL DISORDERS:

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

For secondary amenorrhea, after ruling out pregnancy, NU-MEDROXY tablets may be taken in doses ranging from 5 to 10 mg daily for 12 to 14 days per cycle 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 NU-MEDROXY.

b) Dysfunctional uterine bleeding (abnormal uterine bleeding):

For dysfunctional uterine bleeding, NU-MEDROXY may be taken in doses ranging from 5 to 10 mg daily for 10 to 14 days beginning on the assumed or calculated 12^{th} to 16^{th} 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 NU-MEDROXY. 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 will be done to rule out the possibility of uterine disease.

You may take NU-MEDROXY with or without food.

Some medications can interfere with the action of NU-MEDROXY and NU-MEDROXY can interfere with the action of other medications. Some examples of medications which may interact with NU-MEDROXY are aminoglutethimide, rifampin, antipyrine, warfarin, digitoxin, carbamazepine, phenytoin and St. John's Wort. When you are taking NU-MEDROXY 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: In female patients, over dosage may result in abnormal discontinuation of menstrual periods followed by irregular menstrual periods for several cycles. No cases of over dosage in male patients have been reported.

Treatment: In the case of accidental over dosage, contact your doctor, your nearest hospital emergency department and/or your local Poison Control Centre immediately. Show the doctor the bottle of tablets and any other medications you are taking.

PHARMACEUTICAL INFORMATION

What does NU-MEDROXY contain? Each tablet of NU-MEDROXY contains the active ingredient medroxyprogesterone acetate (2.5 mg or 5 mg) as well as the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, sodium lauryl sulfate and colloidal silicon dioxide.

The 2.5 mg tablet also contains the colouring agents D&C yellow #10 and FD&C yellow #6. The 5 mg tablet also contains the colouring agent FD&C blue #2.

STORAGE

How to store NU-MEDROXY

- KEEP OUT OF THE REACH OF CHILDREN
- Store at room temperature (15 to 30°C).
- Do not store in damp places. Heat or moisture may cause the medicine to break down.
- Do not use medication that has passed its expiry date.

PHARMACOLOGY

Medroxyprogesterone acetate induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. Medroxyprogesterone acetate induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests, medroxyprogesterone acetate has some adrenal corticoid-like activity; in dogs, it increases serum growth hormone levels.

CLINICAL PHARMACOLOGY

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

Endocrine

Medroxyprogesterone acetate in appropriate doses, suppresses the secretion of pituitary gonadotropins which in turn, prevents follicular maturation, producing anovulation in the pre-menopausal woman.

Medroxyprogesterone acetate in appropriate doses suppresses the Leydig cell function in the male (i.e., suppresses endogenous testosterone production).

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 (E_2DH) activity, the enzyme mechanism by which endometrial cells metabolize and excrete estrogens.

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.

TOXICOLOGY

ANIMAL STUDIES

Acute Toxicity

The oral LD_{50} of medroxyprogesterone acetate was found to be greater than 10,000 mg/kg in the mouse. The intraperitoneal LD_{50} in the mouse was 6985 mg/kg.

Sub-acute and Chronic Toxicology

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

Medroxyprogesterone acetate was administered orally to dogs and rats at 3, 10 and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher doses.

CARCINOGENICITY

Long-term toxicology studies in the monkey, dog, and rat with parenteral medroxyprogesterone acetate have disclosed:

1) No uterine or breast abnormalities were revealed in the rat after 2 years.

2) Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days, for 7 years, developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger,

persistent, and more numerous. In addition, 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.

3) No uterine malignancies were found in monkeys receiving placebo, 3 mg/kg, or 30 mg/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 30 mg/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

In the Salmonella/Microsome test (Ames test), DNA damage/alkaline elution assay, and micronucleus test, medroxyprogesterone acetate showed no mutagenic properties.

REPRODUCTION AND TERATOLOGY

Animal studies have not demonstrated 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.

Medroxyprogesterone acetate produced cleft palates in rabbits, but has been attributed to that particular species' sensitivity to the drug's glucocorticoid activity.

Medroxyprogesterone acetate given orally at 1, 10, and 50 mg/kg/day in pregnant Beagle bitches produced clitoral hypertrophy in the female pups of the high-dose animals. No abnormalities were noted in any of the male pups.

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

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