PRODUCT MONOGRAPH

[PR] GEN-MEDROXY

Medroxyprogesterone Acetate Tablets USP

2.5 mg, 5 mg and 10 mg

PROGESTAGEN-PROGESTATIONAL STEROID

GENPHARM INC.
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PRODUCT MONOGRAPH

[PR] GEN-MEDROXY

(Medroxyprogesterone Acetate Tablets, USP)

2.5 mg, 5 mg and 10 mg

PHARMACOLOGIC CLASSIFICATION

PROGESTAGEN-PROGESTATIONAL STEROID

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:

- Estrogen 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

GEN-MEDROXY (medroxyprogesterone acetate), an orally-active progestational steroid, when administered to women with adequate endogenous estrogen, transforms a proliferative endometrium into a secretory endometrium. **GEN-MEDROXY** inhibits the secretion of pituitary gonadotropin which, in turn, prevents follicular maturation and ovulation.

It has been well established that endometrial hyperplasia experienced by a large number of post-menopausal women receiving estrogen only therapy is caused primarily by the action of estrogen on the uterus in the absence of progesterone. This unchecked growth of the endometrium significantly increases the risk among those women with an intact uterus of developing endometrial cancer. Therefore, for women with intact uteri, progestin therapy is added to estrogen therapy to protect against endometrial hyperplasia.

Pharmacokinetics

Absorption

Medroxyprogesterone acetate is rapidly absorbed from the gastrointestinal tract with peak plasma levels achieved by approximately 4 hours.

Metabolism

Medroxyprogesterone acetate is metabolized in the liver to several progestin metabolites. The principal metabolite identified is 6-alpha-methyl-6-beta, 17 alpha, 21-trihydroxy-4-pregnene-3,20-dione-17-acetate, which is excreted in the urine.

Distribution

Medroxyprogesterone acetate is approximately 90% protein bound, primarily to albumin.

Excretion

Medroxyprogesterone acetate is primarily eliminated via fecal excretion. Approximately 44% of an oral dose is eliminated through urinary excretion, mainly as glucuronide conjugates.

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

PIVOTAL CLINICAL TRIALS

Bioequivalence studies were conducted that demonstrate clinical equivalence of Gen-Medroxy with the Canadian reference product and thereby establish the safety and efficacy of Gen-Medroxy. The summary of the comparative bioavailability data are presented in the following section.

BIOAVAILABILITY

In a randomized cross-over study with 25 healthy post-menopausal female volunteers, the bioavailability of **GEN-MEDROXY** (medroxyprogesterone acetate) 10 mg and PROVERA^{R} 10 mg tablets was studied following multiple oral doses in the following regimens:

A) one **GEN-MEDROXY** 10 mg tablet or

B) one PROVERA^{R} 10 mg tablet at 0-hour on Days 1-6.

Each dose was administered during a fasting period which began 10 hours before and lasted until

3 hours after the dose. Treatment phases were separated by a 16-day washout period. Blood samples were collected prior to dosing on Days 1-6, and at the following times after drug administration on Day 6: 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 5, 8, 12, 24 and 36 hours. The resulting plasma samples were analyzed for medroxyprogesterone using a radio-immunoassay procedure.

Relevant bioavailability parameters are included in the following Table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA FOLLOWING ORAL ADMINISTRATION

GEN-MEDROXY
(6 Daily Doses of 10 mg)
From Measured Data
Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	TEST	REFERENCE ***	RATIO OF MEANS
AUC_τ* (ng•hr/mL)	**59.56 62.053 (28.2%)**	**60.59 62.546 (26.0%)**	**98.3**
C_{max} (ng/mL)	**6.842 7.2055 (33.5%)**	**6.676 7.0346 (31.8%)**	**102.5**
C_{min} (ng/mL)	**1.145 1.2183 (34.6%)**	**1.144 1.2041 (32.0%)**	**100.1**
Fluctuation (%)**	**235.87 (28.9)**	**226.32 (30.1)**	

***** **τ = 24 hours**
****** **For fluctuation, the values are arithmetic mean (CV%)**
******* **Upjohn (Provera7) medroxyprogesterone acetate tablets. The Upjohn Company of Canada, Canada.**

INDICATION AND CLINICAL USES

GEN-MEDROXY (medroxyprogesterone acetate) is indicated for the following conditions:

1. **for hormonal replacement therapy, to oppose the effects of estrogen on the endometrium;**
2. **functional menstrual disorders due to hormonal imbalance in non-pregnant women, in the absence of organic pathology.**

CONTRAINDICATIONS

GEN-MEDROXY (medroxyprogesterone acetate) **by itself or in combination with estrogen** is contraindicated in patients with any of the following disorders:

1. Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis.
2. Known or suspected hypersensitivity to **GEN-MEDROXY or to any component of the product (see PHARMACEUTICAL INFORMATION)**.
3. Undiagnosed abnormal genital bleeding.
4. Undiagnosed urinary tract bleeding.
5. Known or suspected pregnancy (either for diagnosis or therapy). (See **WARNINGS**)
6. Active hepatic dysfunction or disease, especially of the obstructive type.
7. Personal history of known or suspected estrogen/progestin-dependent neoplasia such as breast or endometrial cancer.
8. Endometrial hyperplasia.
9. Active or past history of cerebral apoplexy or arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease).
10. Classical migraine.
11. Partial or complete loss of vision due to ophthalmic vascular disease.

Note: If used alone (not in combination with estrogen therapy), medroxyprogesterone acetate is not contraindicated in patients with endometrial hyperplasia.

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 trials, 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 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.

Please note: 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/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=.01).

Additional Warnings

Discontinue medication pending examination, if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

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 GEN-MEDROXY during pregnancy or if she becomes pregnant while taking the drug, she should be appraised of the potential risk to the fetus.**

Clinical suppression of adrenocortical function has not been observed at low dose levels; however, at the very high doses (500 mg daily or more) of medroxyprogesterone acetate used in the treatment of certain cancers, corticoid-like activity has been reported. **In some cases it can produce Cushingoid symptoms (e.g., "moon" facies, fluid retention, glucose intolerance and blood pressure elevations).**

Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. **Infants exposed to GEN-MEDROXY 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 **GEN-MEDROXY**.

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.

PRECAUTIONS

1. Before **GEN-MEDROXY** is administered the patient should have a complete physical examination including a blood pressure examination. 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.

2. 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.**

3. 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.

4. Because 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 disease associated with hypercalcemia and in patients with renal insufficiency.

5. 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.

6. 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.

7. Patients should be advised of menstrual bleeding patterns expected with the sequential regimen. (see Dosage and Administration). Upon sequential administration of GEN-

MEDROXY to women with adequate levels of estrogen (endogenous or exogenous), withdrawal bleeding occurs within 7 days after stopping GEN-MEDROXY treatment. Bleeding that occurs during GEN-MEDROXY treatment indicates a need for a longer duration or a higher dose of GEN-MEDROXY.

8. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. **Some patients may complain of premenstrual like depression while on GEN-MEDROXY**.

9. A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri and post-menopausal patients on progestogens. The mechanism of this is obscure. For this reason, 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.

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

11. Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.

12. 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.

13. Women with familial hypertriglyceridemia or porphyria need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

14. 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**.

Drug Interactions

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

Concomitant administration of aminoglutethimide with **GEN-MEDROXY** [medroxyprogestrone acetate (MPA)], may significantly reduce the bioavailability of MPA.

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

In one published study of 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. Half-lives decreased for antipyrine and increased for warfarin. The decrease observed in warfarin clearance may be of clinical importance. Coagulation tests should be appropriately monitored.

Metabolism of MPA is catalyzed by the cytochrome P450 enzymes. Carbamazepine, phenobarbital, primidone and phenytoin are inducers of cytochrome P450 enzymes and may theoretically increase the metabolism of MPA resulting in the decrease in serum concentration and reduce the effectiveness of MPA.

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.

Interactions of MPA with acetylsalicylic acid, dipyridamole and heparin are not documented in published literature.

Laboratory Tests

The following laboratory tests may be affected by the use of **GEN-MEDROXY USP:**

a) Gonadotropin levels
b) Plasma progesterone levels
c) Urinary pregnanediol levels
d) Plasma testosterone levels (in the male)
e) Plasma estrogens level (in the female)
f) Plasma cortisol levels
g) Metyrapone test
h) Glucose tolerance test
i) Lipoprotein levels

Altered test results may be an indication of an underlying condition. Discontinuation of **GEN-MEDROXY** may be warranted and laboratory tests should be repeated.

Please note: 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 neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been associated with the use of **GEN-MEDROXY** by itself or in combination with estrogen:

Gastrointestinal

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

Genitourinary

Breakthrough bleeding; spotting; changes 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 and Mucous Membranes

Sensitivity reactions ranging from itching to generalized rash and anaphylaxis; chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; pruritus; urticaria; angioneurotic edema; 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; insomnia; somnolence; pre-menstrual syndrome like symptoms; 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; pyrexia; "moon" facies; musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

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

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 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.

Treatment

There is no known therapy for overdosage of medroxyprogesterone. **Where overdosing occurs, symptomatic treatment should be administered**.

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. **GEN-MEDROXY** (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 **GEN-MEDROXY**, should be considered.

    A positive test is indicated by the presence of withdrawal bleeding which occurs within 7 days after stopping **GEN-MEDROXY** treatment. Withdrawal bleeding implies the

presence of sufficient endogenous estrogen to stimulate the endometrium. **GEN-MEDROXY** 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 **GEN-MEDROXY**, should be considered.

b) Sequential Therapy:

<table>
<tr><td 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</td></tr>
<tr><td colspan="2">Sequential Estrogen - 25 days</td><td colspan="2"></td></tr>
<tr><td></td><td>Start</td><td>GEN-MEDROXY
5-10 mg/day</td><td></td></tr>
<tr><td colspan="4">Continuous Estrogens - everyday</td></tr>
<tr><td>GEN-MEDROXY
5-10 mg/day</td><td>Stop</td><td colspan="2"></td></tr>
</table>

In women with an intact uterus receiving estrogen replacement therapy, **GEN-MEDROXY** tablets may be given in a dosage of 5 - 10 mg daily for 12 - 14 days. The recommended starting dose for **GEN-MEDROXY** should be 10 mg/day, administered for 12 - 1 4 days. A dose of 5 mg/day **GEN-MEDROXY** for 12 - 14 days may be appropriate for some women.

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

2. **Functional Menstrual Disorders**

a) **Secondary Amenorrhea:**

After ruling out pregnancy, GEN-MEDROXY may be employed in doses ranging from 5 to 10 mg daily depending upon the degree of endometrial stimulation desired. The dose should be given daily for 10 days beginning on the assumed 16th day of the cycle.

In patients with poorly developed endometria, conventional estrogen therapy should be given in conjunction with **GEN-MEDROXY**.

Withdrawal bleeding usually occurs within 3 days after combined estrogen and **GEN-MEDROXY** therapy.

Progestogen-induced withdrawal bleeding should occur within 3 to 7 days following discontinuation of the progestogen in the presence of an endometrium that has been previously proliferated by endogenous estrogen.

b) **Dysfunctional Uterine Bleeding:**

In dysfunctional uterine bleeding, GEN-MEDROXY may be given in doses ranging from 5 to 10 mg for 10 days beginning on the assumed or calculated 16th day of the cycle.

When bleeding is due to a deficiency of both ovarian hormones, as indicated by a poorly developed proliferative endometrium, estrogens should be used in conjunction with **GEN-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 diagnostic measures should be undertaken to rule out uterine pathology.

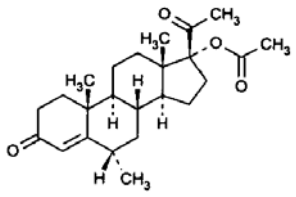
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Medroxyprogesterone Acetate

Chemical Name: 1) Pregn-4-ene-3,20-dione,17-(acetyloxy)-6-methyl-,(α)-;
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 209°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

GEN-MEDROXY (2.5, 5 and 10 mg) also contain the following inactive ingredients: lactose, magnesium stearate, methylcellulose and microcrystalline cellulose. The colouring agents are D&C Red # 30 and D&C Yellow # 10 for the 2.5 mg (peach) and FD&C Blue # 1 for the 5 mg tablet (blue).

STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature 15-30ºC.

AVAILABILITY OF DOSAGE FORMS

GEN-MEDROXY (medroxyprogesterone acetate) tablets are available as:

- 2.5 mg (peach) oval tablets, scored on one side and debossed with “G2.5" the reverse side, in bottles of 100 and 500.
- 5 mg (blue) oval tablets, scored on one side and debossed with “G5" on the reverse side, in bottles of 100 and 500.
- 10 mg (white) oval tablets, scored on one side and debossed with “G10" on the reverse side in bottles of 100 and 500.

PATIENT INFORMATION

Please read this PATIENT INFORMATION before you start using [Pr]GEN-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 pharmacist.

WARNING

Extensive studies were carried out by the Women's Health Initiative that compared a group of post-menopausal women receiving long term treatment with combined estrogen and progestin hormone therapy to a group of women receiving placebo (sugar pill). The studies indicated an increased risk of heart attack, stroke, invasive breast cancer, and blood clotting in both legs and lungs among the post-menopausal women receiving the estrogen/progestin treatment. In light of these findings it is highly recommended that the following be 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.**

INTRODUCTION: What is GEN-MEDROXY?

GEN-MEDROXY (medroxyprogesterone acetate) is a progestin substance that controls the excessive build-up of tissue in the lining of the uterus (womb). This build-up is caused by the presence of the hormone estrogen combined with a lack of the hormone progesterone. If left unchecked, this tissue buildup results in thickening of the lining of the uterus and could lead to abnormalities in normal menstrual function as well as to the development of cancer of the uterus.

GEN-MEDROXY acts to reduce this thickening of the lining of the uterus to substantially reduce the risk of certain menstrual disorders and to reduce the risk of cancer of the uterus. **GEN-**

MEDROXY is therefore added to estrogen therapy to counter the undesirable effects of estrogen on the lining of the uterus.

This medicine is available in 2.5, 5 and 10 mg tablets. When used as an important component of hormone replacement therapy (HRT) for post-menopausal women who have not had a hysterectomy (surgical removal of the uterus), GEN-MEDROXY should be taken as 5 to 10 mg per day for 12 to 14 days of each cycle, starting with day 1 of the cycle, as prescribed by your doctor.

For treatment of functional menstrual disorders, GEN-MEDROXY should be taken as 5 to 10 mg per day for 10 days of each cycle, beginning on the assumed 16th day of the cycle, or as prescribed by your doctor.

Please note: HRT has been associated with an increased risk of developing invasive breast cancer, coronary heart disease, and blood clotting complications in both legs and lungs. HRT should therefore be used only under the supervision of a physician, with regular follow-up at least once per year to identify any adverse events associated with its use.

INDICATIONS: GEN-MEDROXY is approved for use in the following situations:

1. For hormonal replacement therapy, to oppose the effects of estrogen on the lining of the uterus.
2. Functional menstrual disorders due to hormonal imbalance in non-pregnant women, in the absence of disease.

HRT is prescribed as either an estrogen only or combination estrogen/progestin therapy, depending on whether the woman being prescribed the therapy has an intact uterus. If you have an intact uterus, a combination estrogen and progestin therapy is prescribed in order that progestin

can control the negative effect of estrogen on the uterus. If you have had a hysterectomy (surgical removal of the uterus), you will not require progestin therapy in addition to your estrogen therapy since there is no longer a concern with the unwanted effects estrogen can have on the uterus.

It is therefore important to note that if you are prescribed HRT, and have not had a hysterectomy (removal of the uterus), you should talk to your doctor about having progestin prescribed in association with any estrogen product you are taking.

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

GEN-MEDROXY, by itself or in combination with estrogen should not be taken if you:

1. Have active liver disease.
2. Have a personal history of known or suspected estrogen/progestin-dependent cancer such as breast cancer or cancer of the uterus.
3. Have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus). 4. Have experienced any undiagnosed or unexpected vaginal bleeding.
5. Have experienced any undiagnosed or unexpected urinary tract bleeding.
6. Are pregnant or suspect you may be pregnant.
7. Have a history of heart disease (including heart attack) or stroke.
8. Experience migraine headaches.
9. Have a history of blood clots or active thrombophlebitis (inflammation of the veins).
10. Have a history of partial or complete loss of vision due to blood vessel disease of the eye.
11. Have had an allergic or unusual reaction to GEN-MEDROXY or to any of its ingredients (see **PHARMACEUTICAL INFORMATION**).

Note: Endometrial hyperplasia is not a restriction on use if medroxyprogesterone acetate is used alone (not in combination with estrogen therapy).

WARNINGS AND PRECAUTIONS

Warnings

See Boxed Warnings at the front page

In deciding whether to use **GEN-MEDROXY**, there are certain factors that you should consider regarding the risks involved. Discuss with your doctor how the risks associated with taking this medication, either by itself or in conjunction with estrogen, weighs against the benefits you will get from taking it. Use this as the basis for your decision.

Some of the risks found to be associated with the use of progestins (like **GEN-MEDROXY**), either by themselves or in combination with estrogen are:

Cardiovascular disorders

Long term studies conducted by the Women's Health Initiative indicate that there are increased risks of stroke and coronary heart disease associated with the use of estrogen with or without progestin. These studies concluded that there are more risks than benefits among women using combined Hormone Replacement Therapy (conjugated equine estrogens/medroxyprogesterone acetate), compared to the group taking a placebo (sugar pill).

Breast cancer

Long term studies conducted by the Women's Health Initiative indicate that there are increased risks of invasive breast cancer associated with the use of estrogen with or without progestin. These studies concluded that there are more risks than benefits among women taking combined Hormone Replacement Therapy (HRT), compared to the group taking a placebo (sugar pill).

Hormone replacement therapy (HRT) 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 HRT.

It is therefore recommended that you undergo a mammography before the start of HRT treatment and at regular intervals during treatment, as ordered by your doctor, and that you discuss the risks and benefits of long term treatment with your doctor, and the importance of self- examination of the breast.

Venous thromboembolism (blood clots)

Long term studies conducted by the Women's Health Initiative indicate that there are increased risks of blood clots in the leg veins and in the lungs associated with the use of estrogen with or without progestin. These studies concluded that there are more risks than benefits among women taking combined Hormone Replacement Therapy (HRT), compared to the group taking a placebo (sugar pill).

Other risk factors for this condition include age, personal or family history of blood clots, obesity and smoking. Factors which may temporarily increase risk include prolonged immobilization, major elective surgery or posttraumatic surgery, or major trauma.

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).

Precautions

Before you start taking GEN-MEDROXY, you should have a pre-treatment physical examination, including a blood pressure check, a breast exam, a pelvic exam and Pap test. It is important that your doctor rule out the presence of breast cancer or genital cancer before you start taking this medication. Your doctor may also recommend that you have a mammogram (breast x-ray) and some blood tests (blood sugar, calcium, triglycerides, cholesterol and liver function) before you start treatment.

Your doctor will also discuss with you the need for frequent follow-up examinations, the first of

which should be done within 3-6 months after starting the treatment to assess your response to the treatment. Thereafter, follow-up examinations should be done at least once a year and should include at least those procedures outlined above. **Before starting treatment with GEN-MEDROXY, either by itself or in combination with estrogen, you should 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 been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus)
- have experienced undiagnosed or abnormal vaginal bleeding
- have experienced undiagnosed or abnormal urinary tract bleeding
- have been diagnosed with endometriosis
- have a history of heart disease (including heart attack) or stroke
- experience migraine headaches
- have a personal or family history of blood clots 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
- are currently breast feeding
- have had an allergic response or unusual reaction to any of the ingredients of GEN-MEDROXY (see **PHARMACEUTICAL INFORMATION**), or to other medications or other substances
- smoke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with 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.
- are taking any other prescription medications, over-the-counter medications or herbal products

While taking **GEN-MEDROXY** (medroxyprogesterone acetate), by itself or in combination with estrogen, you should be aware of the following:

- Stop using this medication if you are diagnosed with blood clots of any sort, including those of the limbs, lungs or eyes. Should any of these occur or be suspected, your doctor will discontinue treatment and investigate the cause.

- Stop using medication if you experience sudden partial or complete loss of vision, or if you experience sudden onset of double vision or migraine headache. Inform your doctor immediately.

- Inform your doctor if you become pregnant while using this drug as there might be a potential risk to the fetus**.**

- Inform your doctor immediately of any incidence of seizures, loss of consciousness, asthma, allergic reactions or suspected reactions to the medication, vaginal bleeding, depression, or elevations in your blood pressure. Should any of these occur or be suspected, your doctor will carefully reassess your need to continue therapy.

ADVERSE EFFECTS

See also **WARNINGS AND PRECAUTIONS.**

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

any other unusual symptoms:

Gastrointestinal

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

Genital Bleeding/spotting

Genital bleeding; genital spotting; changes in menstrual flow; vaginal itching/discharge; pain during sexual intercourse; pain during urination; pre-menstrual-like syndrome; cervical secretions.

Skin and Mucous Membranes

Sensitivity reactions ranging from itching and hives to generalized rash and anaphylaxis (severe, potentially life-threatening allergic reaction): changes to face pigmentation; loss of scalp hair; acne.

Breast Tenderness

Breast swelling and tenderness.

Cardiovascular/Hematologic

Palpitations; blood clotting problems; more pronounced varicose veins; increase in blood pressure

Central Nervous System

Aggravation of migraine episodes; headaches; mental depression; nervousness; dizziness; fatigue; irritability; not being able to sleep; sleeping too much; pre-menstrual syndrome like symptoms.

Ophthalmic

Visual disturbances; eye discomfort due to lesions; intolerance to contact lenses.

Other

Changes in appetite; changes in body weight; swelling and puffiness in the face and/or limbs; change in libido; fever; musculoskeletal pain including leg pain; increased blood sugar levels.

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

HOW TO USE

GEN-MEDROXY is used in hormone replacement therapy and for treating functional menstrual disorders.

1. **Hormone Replacement Therapy:**

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

2. **Functional Menstrual Disorders**

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

After ruling out pregnancy, GEN-MEDROXY may be taken in doses ranging from 5 to 10 mg daily as recommended by your doctor. The dose should be given daily for 10 days beginning on the assumed 16th day of the cycle.

If your doctor determines that you have a poorly developed uterine lining, conventional estrogen therapy should be given in conjunction with **GEN-MEDROXY**.

b) **Dysfunctional Uterine Bleeding (abnormal uterine bleeding):**

In dysfunctional uterine bleeding, GEN-MEDROXY may be taken in doses ranging

from 5 to 10 mg for 10 days beginning on the assumed or calculated 16th day of the cycle. When bleeding is due to a deficiency of both estrogen and progestin, as determined by your doctor, estrogens should be used in conjunction with **GEN-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.

3. **Effect of Food:**

GEN-MEDROXY is best taken immediately before and after meals.

4. **Actions of Other Medications:**

Some medications can interfere with the action of GEN-MEDROXY and GEN-MEDROXY can interfere with the actions of other medications. When you are taking GEN-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 OVER DOSAGE

Symptoms

If you overdose on **GEN-MEDROXY**, you may experience a feeling of depression, tiredness, develop acne, and abundant growth of body hair. For female patients, you might also notice disruptions in your menstrual cycle, starting with a lack of menstruation for an extended period, followed by irregular menses for several cycles.

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.

Treatment

There is no known therapy for overdosage of **GEN-MEDROXY**. **In the case of an overdosage, you should call your doctor and/or your local Poison Control Center.**

PHARMACEUTICAL INFORMATION

Medicinal Ingredients:	Medroxyprogesterone acetate
Non-medicinal Ingredients:	Lactose, methylcellulose, microcrystaline cellulose, magnesium stearate, colour (D&C yellow#10, blue #1 & red#30).

STORAGE

- Keep this medicine out of the reach of children
- Store at controlled room temperature (15-30 °C), away from heat and moisture (heat or moisture may cause the medicine to break down).
- Discard medicine if it has passed its expiry date or if it is no longer needed.

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 animals tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

CLINICAL PHARMACOLOGY

Medroxyprogesterone acetate is a progestational agent devoid of androgenic and estrogenic activity. Medroxyprogesterone acetate in appropriate doses, suppresses the secretion of pituitary gonadotropins which in turn, prevents follicular maturation, producing an ovulation in the reproductive aged woman.

Medroxyprogesterone acetate in appropriate doses suppresses the Leydig cell function in the male,

i.e., suppresses endogenous testosterone production.

A dose of either 5 or 10 mg of Medroxyprogesterone acetate given daily for 10 days has the equivalent effect of 20 mg of parenteral progesterone given daily for 10 days in producing an optimal secretory change in an estrogen primed endometrium. 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.

Patients with the Pickwickian Syndrome; chronic Mountain sickness and some patients with chronic obstructive pulmonary disease reduce their hypercapnia when treated with oral medroxyprogesterone acetate (through a centrally-mediated stimulation of ventilatory drive).

Like progesterone, medroxyprogesterone acetate 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 manifest.

Pharmacokinetics

The pharmacokinetics of medroxyprogesterone acetate were investigated in rats following oral

administration of single 0.2, 1.0, 5.0, and 20.0 mg/kg doses. The resulting pharmacokinetic parameters are listed in Table 1.

TABLE 1. PHARMACOKINETIC VALUES OF MEDROXYPROGESTERONE ACETATE IN RATS FOLLOWING SINGLE-DOSE ADMINISTRATION

Medroxyprogesterone acetate dose (mg/kg)	Route	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng•g/mL)	$t_{1/2}$ (h)
0.2	i.g.	8.5	107	10.4
1.0	i.g.	45.6	545	9.7
5.0	i.g.	378	2536	10.2
20.0	i.g.	1062	8007	8.0

Medroxyprogesterone acetate was readily absorbed. Peak plasma medroxyprogesterone acetate levels occurred at 3, 2, 1.5, and 3 hours for the 0.2, 1, 5, and 20 mg/kg dosages, respectively. A linear response was observed in the plasma medroxyprogesterone acetate $AUC_{0-\infty}$ values over the dose range of 0.2 to 5.0 mg/kg. However, the $AUC_{0-\infty}$ values for the 20 mg/kg dose were slightly lower than anticipated. Elimination half-lives remained essentially constant over the dose range studied.

The pharmacokinetics of medroxyprogesterone acetate were also determined in rats following oral administration of medroxyprogesterone acetate at 0.2, 5, and 20 mg/kg daily for 14 days. Mean C_{max}, AUC_{0-24}, concentration at 24 hours (C_{24}) and $T_{1/2}$ values after 14 days of dosing are presented in Table 2.

TABLE 2. MEAN C_{max}, AUC_{0-24}, and $T_{1/2}$ VALUES IN RATS AFTER 14 DAYS OF MEDROXYPROGESTERONE ACETATE TREATMENT

Medroxyprogesterone acetate dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24} (ng•g/mL)	$t_{1/2}$ (h)
0.2	10.2	101.0	14.7
5.0	456.3	1982.4	11.0
20.0	550.2	3596.2	13.7

The peak plasma medroxyprogesterone acetate concentrations on treatment day 14 occurred at 1.5 hours for all doses (0.2, 5.0 and 20 mg/kg). Mean C_{max} values for the 0.2 and 5.0 mg/kg doses were higher after multiple doses than after single dose administration. However, the mean C_{max} values after multiple doses of 20 mg/kg dose was 52% of the C_{max} values after the single dose. Based on an elimination $t_{1/2}$ of 15 hours and a 24-hour dose interval, an accumulation factor of 1.4 is predicted for the 0.2 mg/kg dose. The day 14 AUC_{0-24} from the 0.2 mg/kg dose was similar to the $AUC_{0-\infty}$ value after single dose administration. At the 5 and 20 mg/kg doses, mean AUC_{0-24} values were less than the $AUC_{0-\infty}$ from the single-dose study. The relative decrease in AUC values for the 5 and 20 mg/kg dose is likely to be due to autoinduction of medroxyprogesterone acetate metabolism.

The drug was given in the diet admixture in rat carcinogenicity study; therefore the absorption of the drug was investigated following a 14-day multiple dose/feed study in female rats. Medroxyprogesterone acetate was mixed in the feed. The doses were 0.2 and 20 mg/kg/day. Mean plasma medroxyprogesterone acetate levels from the two sampling times for the 0.2 mg/kg/day dose were 4.9 ng/mL (PM) and 5.3 ng/mL (AM), and for the 20 mg/kg/day dose were 133.5 ng/mL (PM) and 231.0 ng/mL (AM).

If the values at these two time points are presumed to represent average plasma medroxyprogesterone acetate levels over the respective 12-hour cycles, the steady-state AUC

values over a 24-hour period are estimated to be 122.4 and 4374 ng•h/mL for the 0.2 and 20.0 mg/kg/day doses, respectively. These values are 20% greater than the AUC values after daily doses by oral gavage, indicating good absorption from the feed.

TOXICOLOGY

ANIMAL STUDIES

Acute Toxicity: The oral LD_{50} of medroxyprogesterone acetate as reported in the literature is as follows:

Species	Route	Study Type	LD_{50}	Effect
rat	oral	LD_{50}	>6.4 g/Kg	Details not reported
mouse	oral	LD_{50}	>16 g/Kg	Details not reported
dog	oral	LD_{50}	>5 g/Kg	Details not reported

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.

Reproduction Studies: 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. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

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

1. 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, more numerous, persistent and there were two high dose animals that developed breast malignancies.

2. Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in three of the monkeys in the 30 mg/kg group. Upon histopathologic examination these nodules were determined to be hyperplastic. The occurrence of the lesions in these two monkeys does not signify that medroxyprogesterone acetate is carcinogenic in women.

3. No uterine or breast abnormalities were revealed in the rat after 2 years. The micronucleus test and the salmonella/microsome test (Ames Assay) have not shown medroxyprogesterone acetate to be a mutagen. Animal studies have not confirmed any impairment of fertility in first or second generation studies.

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

Two Year Oral (Diet) Carcinogenicity Study - Rat

In a study conducted by Wyeth-Ayerst, medroxyprogesterone acetate administered in the diet to

female Charles River CD rats (approximately 6 weeks of age at treatment initiation) for 104 to 106 consecutive weeks. Dosages tested were 0, 0.2, 1.0, and 5.0 mg/kg.

Many of the deaths occurring in this study were associated with spontaneous age-related changes; however, in the 5.0 mg/kg group, there was a drug-related decrease in survival, as shown in Table 3.

TABLE 3. SURVIVAL IN RATS GIVEN Medroxyprogesterone acetate

	Medroxyprogesterone acetate (mg/kg)			
	0 (n = 200)	0.2 (n = 100)	1.0 (n = 100)	5.0 (n = 100)
Survival	34%	40%	38%	20%
Number of Deaths	132	60	62	80

Other drug-related findings in this study included adrenal cortical atrophy, ovarian atrophy, uterine atrophy, chronic progressive nephropathy (CPN), and cardiomyopathy. The administration of medroxyprogesterone acetate to rats may induce atrophy of the adrenal cortex, ovaries, and uterus by acting on the pituitary gland and/or hypothalamus to reduce the production of gonadotropin and adrenocorticotropin. A significant increase in group mean body weight occurred during the first year in the medroxyprogesterone acetate-fed rats. A correlation exists between early body weight gain and increased incidence of CPN and cardiomyopathy in rats.

The preneoplastic changes included uterine endometrial gland hyperplasia and islet cell hyperplasia, which occurred predominantly in the middle- and high-dosage groups in a dose-related manner. The neoplastic changes included an increased incidence of islet cell carcinoma and adenoma and a decreased incidence of islet cell carcinoma and adenoma and a decreased incidence of mammary gland tumors, as shown in Table 4. This latter finding may be linked to the significant decrease in serum prolactin concentration observed in the rats in this study[44].

TABLE 4. PERCENTAGE OF MEDROXYPROGESTERONE ACETATE
-TREATED RATS WITH PANCREATIC LESIONS

	Medroxyprogesterone acetate (mg/kg)			
	0 **(n = 196)**	0.2 **(n = 97)**	1.0 **(n = 98)**	5.0 **(n = 100)**
Islet cell carcinoma	**2**	**1**	**5**	**6**
Islet cell adenoma	**5**	**3**	**8**	**18**
Islet cell hyperplasia	**1**	**1**	**3**	**10**

There is no evidence in the literature that medroxyprogesterone acetate causes pancreatic islet cell neoplasia. Administration of medroxyprogesterone acetate to women should not result in islet cell hyperplasia or neoplasia similar to that observed in the rat for the following reasons:

- The endocrine system of rats is generally more sensitive to hormonal imbalances than humans. In rodents, several different types of endocrine cells (e.g., thyroid follicular cells, adrenal medullary cells, ovarian cortical cells) are more likely to undergo neoplastic transformation in response to the long-term stimulation that results from hormonal imbalance induced by xenobiotic chemicals (especially very high doses of hormones) or physiologic perturbations than are the corresponding cell populations in human.
- When medroxyprogesterone acetate is combined with estrogen, more progesterone receptors are produced and more receptors are available to bind medroxyprogesterone acetate. In the absence of estrogen, fewer progesterone receptors are available to bind medroxyprogesterone acetate, thus leaving more medroxyprogesterone acetate free to bind to glucocorticoid receptors.

- The rats in the middle- and high-dosage groups developed pancreatic islet cell lesions because of continuous exposure to the drug at levels approximately 10 and 50 times greater than AUC values for women receiving a 10 mg oral dose.

The increased incidence of pancreatic islet cell hyperplasia and neoplasia may be related to the cortisol-like activity of progestogens, including medroxyprogesterone acetate. Cortisol increases serum glucose levels, which stimulates the beta cells of the pancreatic islets to produce insulin. Repeated stimulation of the beta islet cells may cause compensatory hyperplasia and neoplasia of the cells. In humans, the diabetogenic response to medroxyprogesterone acetate is slight.

A significant drug-related decrease in mean adrenal, ovarian, uterine, and pituitary gland weights was observed in the 1.0 and 5.0 mg/kg dose groups. With the exception of the pituitary gland, the decreased organ weight correlated with the atrophic lesion noted on microscopic examination. There was a significant drug-related increase in the mean terminal body weight in all dosage groups and also in the absolute kidney, heart, and liver weights in the 1.0 and 5.0 mg/kg dosage groups. The increased weight of the kidney, heart, and liver correlated with the CPN, cardiomyopathy, and fatty change, respectively, as noted on microscopic examination.

All lesions except those in the pancreas were expected findings with administration of medroxyprogesterone acetate. Such lesions have been described in the literature and are not considered to be significant safety issues.

SELECTED BIBLIOGRAPHY

1. Amadori D, Ravaioli R, Ridolfi R, Gentiline P, Tonelli B, Gambi A, Barbanti F. Oral High Dose Medroxyprogesterone: A Study in 21 Patients. September 1979; Chemioterapia Oncologica, Anno III 3: 219-223.

2. Ausili-Cefaro GP, Cellini N, Ciarniello V, Trodella L. Preliminary Results on MAP (medroxy-acetate progesteron) Employment Orally Administered in the Advanced Mammary Carcinoma. 1979; Acta Med.Rom. 17, 351-356.

3. Bernardo-Strada MR, Imparato E, Aspesi G, Pavesi L, Robustelli Della Cuna G. Oral High Doses of Medroxyprogesterone Acetate (MPA) in the Treatment of Advanced Breast and Endometrial Carcinoma. 1980; Edizoioni Minerva Medica, 1-6.

4. Bonte J, et al. Cytologic evaluation of exclusive Medroxyprogesterone acetate treatment for vaginal recurrence of endometrial adenocarcinoma. Acta. Cytologica, 1970; 14:6.

5. Brema F, Queirolo MA, Canobbio L, Bruzzi P, Puntoni R, Campora E, Rosso R. Hematologic Parameters During Treatment with High-Dose Medroxyprogsterone. Tumori, 1981; 67:125-128.

6. Canobbio L, Brema F, Massa T, Chiarlone R, Boccardo F, Merlano M. Toxic Effects and Therapeutic Activity of Orally Administered High Dose Medroxyprogesterone Acetate in Metastatic Breast Cancer. September 1979; Chemioterapia Oncologica, Anno III, 3:214-218.

7. Davila E, Thompson TT, Riordan D, Vogel CL. High Dose Oral Medroxyprogesterone Acetate (HDO-MPA) for Advanced Breast Cancer (BC). April 1982; ASCO Abstract (In Press), ASCO 25-27.

8. Glen EM, et al. Biological activity of 6-alpha-methyl compounds corresponding to progesterone, 17 alpha-hydroxyprogesterone and compound S. 1959; Metabolism 8:3.

9. Gold JJ, et al. The use of 6-alpha-methyl 17-acetoxy-progesterone in specific menstrual disturbances. 1961; Brook Lodge Symposium on Progesterone, Brook Lodge Press, Augusta, Michigan 187-200.

10. Hamblen et al. The use of 6-alpha-methyl 17-alpha-acetoxyprogesterone in functional disorders of uterine bleeding and in eugonadotropuric amenorrhea. 1961; Brook Lodge

Symposium on Progesterone, Brook Lodge Press, Augusta, Michigan 201-217.

11. Hellman L, et al. Effect of Medroxyprogesterone on the pituitary-adrenal axis. 1976; J. Clin. Endocrinol. Metab. 42:912-917.

12. Kistner RW, Griffiths CT. Use of progestational agents in the management of metastic carcinoma of the endometrium. 1968; Clin. Obs. Gyn. 11:439-456.

13. Luporini G, Beretta G, Tabiadon D, Tedeschi L, Rossi A. Comparison between oral Medroxyprogesterone (MPA) and tamoxifen (TMX) in advanced breast carcinoma. 1981; Proceedings of American Assoc. for Cancer Research, 22, 72 Meet. 434.

14. Moller KA, Anderson AP. Peroral administration of Medroxyprogesterone (MPA) in advanced cancer of the breast. 1981; Acta Obstet. Gynecol. Scand. Suppl. 101, 47-48.

15. Pannuti F, Burroni P, Fruet F, Piana E, Strocchi E, DiMarco AR, Cricca A, Camaggi CM. Anabolizing and anti-pain effect of the short-term treatment with Medroxyprogesterone (MPA) at high oral doses in oncology. 1980; Panminerva Medica, 22:149-156.

16. Tominaga. Oral high dose Medroxyprogesterone (MPA) in treatment of advanced breast cancer. July 19-24, 1981; 12th International Congress of Chemotherapy, Florence, Italy.

17. ACOG Technical Bulletin #93: Estrogen Replacement Therapy. April 1986.

18. Adachi JD, Anderson C, Murray TM, Prior JC. The Canadian consensus conference on the use of progestins in the menopause II. Effect of progestins on bone. J SOGC 1991;13(1):47-50.

19. Astedt B, Fibrinolytic activity of veins during treatment with medroxyprogesterone acetate. Acta Obstet Gynecol Scand 1972;283-86.

20. Astedt B, On fibrinolysis A. In pregnancy, labour, puerperium and during treatment with sex steroids B. In human ontogenesis and in human organ culture. Acta Obstet Gynecol Scand 1972;51(suppl.18):21.

21. Astedt B, Jeppsson S, Pandolfi M. Fibrinolytic activity of veins during use of depot medroxyprogesterone acetate as a contraceptive. Fertil Steril 1972;23(7):489-92.

22. Back DJ, Breckenridge AM, Crawford F, et al. The effect of rifampicin on norethisterone pharmacokinetics. Europ J Clin. Pharmacol. 1979;15:193-7.

23. Barrett-Connor E, Wingard DL, Criqui MH. Postmenopasual estrogen use and heart disease risk factors in the 1980s: Rancho Bernado, Calif, Revisited. JAMA 1989;261(14):2095-2100.

24. Bewtra C, Kable WT, Gallagher JC. Endometrial histology and bleeding patterns in

menopausal women treated with estrogen and continuous or cyclic progestin. J Reprod Med 1988;33(2):205-8.

25. Council Report: Estrogen Replacement in the Menopause. JAMA 1983;249(3):359-61.

26. FDA Advisory Committee: Estrogen replacement therapy should include a progestin to reduce risk of endometrial cancer advisory committee says; FDA to consider combo NDAs. FDC Reports 1991:11.

27. Ferenczy A, Gelfand MM, Nisker JA, Spence JE. The Canadian consensus conference on the use of progestines in the menopause I. Progestins and the endometrium. J SOGC 1991;13(1):36-42.

28. Gambrell RD Jr. Massey FM, Castaneda TA, Ugenas AJ, Ricci CA, Wright JM. Use of the progestogen challenge test to reduce the risk of endometrial cancer. Obstet Gynecol 1980;55(6):732-38.

29. Gambrell RD Jr, Teran AZ. Changes in lipids and lipoproteins with long-term estrogen deficiency and hormone replacement therapy. AM J Obstet Gynecol 1991;165(2):307-17.

30. Hormone Replacement Therapy: Highlights from the Sixth International Congress on the Menopause. Bangkok, Thailand. Hormone Replacement Therapy 1990:1-8.

31. Lemay A, Wolfe BMJ, Scott JZ, Graves GR. The Canadian consensus conference on the use of progestins in the menopause III. Effects of hormone replacement therapy in the menopause on lipids, lipoproteins and coronary heart disease. J SOGC 1991;13(5):14-20.

32. Murray TM. The importance of estrogen in osteoporosis prevention official position of the Osteoporosis Society of Canada, Bulletin for Physicians 1988;1:7-11.

33. Nachtigall LE, Nachtigall RH, Nachtigall RD, Beckman EM. Estrogen replacement therapy II: A prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. Obstet Gynecol 1979;54(1):74-9.

34. Padwick ML, Pryse-Davis J, Whitehead MI. A simple method for determining the optimal dosage of progestin in postmenopausal women receiving estrogens. N Engl J Med 1986;315(15):930-34.

35. Silfverstolpe G, Gustafson A, Samsioe G, Svanborg A. Lipid metabolic studies in oophorectomized women: effects on serum lipids and lipoproteins of three synthetic progestogens. Maturitas 1982;4:103-11.

36. Swenerton KD, Fugère P, Miller AB, MacLusky N. The Canadian consensus conference on the use of progestins in the menopause IV. Menopausal progestins and breast cancer. J SOGC 1991;13(5):21-5.

37. Tseng L. Steroid specificity in the stimulation of human endometrial estradiol dehydrogenase. Endocrinology 1978;102(5):1398-1403.

38. Tseng L, Gurpide E. Induction of human endometrial estradiol dehydrogenase by progestins. Endocrinology 1975;97(4):825-33.

39. Van Deijk WA, Blijham GH, Mellink WA, Meulenberg PM. Infuence of aminoglutethimide on plasma levels of medroxyprogesterone acetate: Its correlation with serum cortisol. Cancer Treat Rep 1985;69(1):85-90.

40. Weinstein L. Efficacy of a continuous estrogens-progestin regimen in the menopausal patient. Obstet Gynecol 1987;69(6):929-32.

41. Yancy MK, Stone IK, Hannan CJ, Friedl KE, Plymate SR, Wright JR. Serum lipids and lipoproteins in continuous or cyclic medroxyprogesterone acetate treatment in postmenopausal women treated with conjugated estrogens. Fertil Steril 1990;54(5):778-82.

42. Walter L, Ehrhart H, Schuster H, Leonhardt A. Initiation and results of Medroxyprogesterone (MPA) therapy in metastatic breast cancer. 1981; Der Bayerische Internist 3: 21-23.

43. Drug in Japan (Ethical Drugs). Tokyo: Yakugyo Jiko Co., Ltd., 1990; 1196.

44. Zaccheo T, Casazza AM, DiSalle E, Pollini C, DiMarco A. Combined and sequential treatment using FCE21336, a new prolactin-lowering drug, and Medroxyprogesterone (MPA) in DMBA-induced tumors in rats. 1984 Eur. Cancer Clin Oncol 20:1193-7.

45. Gopinath C, Prentice DE, Lewis DJ. The endocrine system. In: Atlas of experimental toxicology pathology. Boston: MTP Press Limited, 1987:104-21.

46. Fraser IS, Weisbert E. A comprehensive review of injectable contraception with special emphasis on depot Medroxyprogesterone acetate. Med J Aust 1981; 1(Suppl 1):1-20.

47. Logothetopoulos J, Sharma BB, Kraicer J. Effects produced in rats by the administration of 6 alpha-methyl-17-alpha-hydroxyprogesterone acetate from birth to maturity. Endocrinology 1961; 68:417-30.

48. Berg BN, Simms HS. Nutrition onset of disease, and longevity in the rat. Can Med Assoc

J 1965; 93:911-3.

49. Turnbull GJ, Lee PN, Roe FJC. Relationship of body weight gain to longevity and to risk of development of nephropathy and neoplasia in Sprague-Dawley Rats. Fd Chem Toxic 1985; 23:355-61.

50. DiCarlo F, Racca S, Conti G. et al. Effects of long-term administration of high doses of Medroxyprogesterone on hormone receptors and target organs in the female rat. J Endocrinol 1984; 103:287-93.

51. Working Paper for Product Monograph of Non Contraceptive Estrogen & Estrogen+Progestin Products, Therapeutic Products Directorate, Bureau of Metabolism, Oncology, and Reproductive Sciences, Reproduction and Urology Division, February 2003

52. James V. Lacey, Jr., Pamela J. Mink, Jay H. Lubin, Mark E. Sherman, Rebecca Troisi, Patricia Hartge, Arthur Schatzkin, and Catherine Schairer, Menopausal hormone replacement therapy and risk of ovarian cancer, .*JAMA* 2002; 288:334-341.

53. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women, Writing Group for the Women's Health Initiative Investigators, JAMA, July, 2002, Vol.288.

54. Kanaya A.M., et al. Glycemic Effects of Postmenopausal Hormone Therapy: The Heart and Estrogen/progestin Replacement Study, A Randomized, Double-Blind, Placebo-Controlled Trial. 2003 Annals of Internal Medicine Vol. 138 pg 1-9.

55. Hulley S, Grady D, Bush T, et al for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998; 280(7):605-613.

56. Grady S, Herrington D, Bittner V, et al for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/progestin replacement study follow-up (HESRS II). JAMA. 2002; 288(1):49-57.

57. Chlebowski RT, Hendrix SL, Langer RD, et al. The Women's Health Initiative randomized trial. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. JAMA. 2003; 289(24):3243-3253.

58. Shumaker SA, Legault C, Rapp SR, et al. The Women's Health Initiative Memory Study: A randomized controlled trial. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. JAMA. 2003; 289(20):2651-2662.

59. Lundgren S, Kvinnsland S, et al. Effect of oral high-dose progestins on the disposition of antipyrine, digoxin, and warfarin in patients with advanced breast cancer. Cancer Chemotherapy Pharmacology (1986) 18: 270-275.

60. Anderson G. A Mechanistic Approach to Antiepileptic Drug Interactions. The Annals of Pharmacotherapy (1998) 32: 554-563.