For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

DEVIRY™ – 10 mg

(Medroxyprogesterone Acetate Tablets I.P)

COMPOSITION

Each uncoated tablet contains:
Medroxyprogesterone Acetate I.P. ……... 10 mg

WARNINGS
CARDIOVASCULAR AND OTHER RISKS

Estrogens with progestins should not be used for the prevention of cardiovascular disease or dementia.

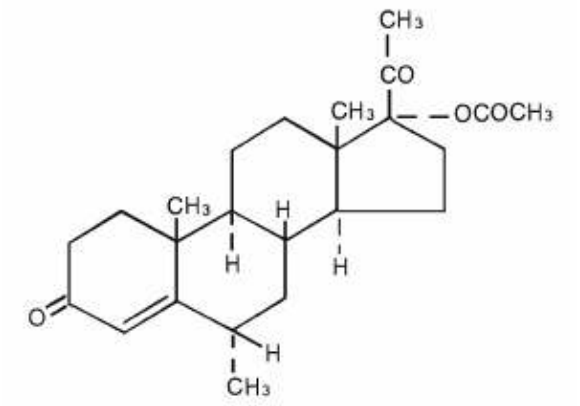
The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Deviry contain medroxyprogesterone acetate, which is a derivative of progesterone. The chemical name for medroxyprogesterone acetate is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. The structural formula is:



CLINICAL PHARMACOLOGY

Pharmacodynamics

Medroxyprogesterone acetate (MPA) administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parentally administered MPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

Pharmacokinetic

A. Absorption:

No specific investigation on the absolute bioavailability of MPA in humans has been reported. MPA is rapidly absorbed from the gastrointestinal tract, and maximum MPA concentrations are obtained between 2 to 4 hours after oral administration.

Administration of Medroxyprogesterone Acetate (MPA) with food increases the bioavailability of MPA. A 10 mg dose of Medroxyprogesterone Acetate (MPA), taken immediately before or after a meal, increased MPA Cmax (50 to 70%) and AUC (18 to 33%). The half-life of MPA was not changed with food.

B. Distribution:

MPA is approximately 90% protein bound, primarily to albumin; no MPA binding occurs with sex hormone binding globulin.

C. Metabolism:

Following oral dosing, MPA is extensively metabolized in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

D. Excretion:

Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates.

E. Special Populations

Renal Insufficiency

The pharmacokinetics of MPA in patients with varying degrees of renal insufficiency have not been reported.

Hepatic Insufficiency

MPA is almost exclusively eliminated via hepatic metabolism. In 14 patients with advanced liver disease, MPA disposition was significantly altered (reduced elimination).

In patients with fatty liver, the mean percent dose excreted in the 24-hour urine as intact MPA after a 10 mg or 100 mg dose was 7.3% and 6.4%, respectively.

F. Drug Interactions

No formal pharmacokinetic drug interaction studies have been reported with Medroxyprogesterone Acetate (MPA)

INDICATIONS

DEVIRY 10 mg is indicated for:

- Menstrual Disorders
- Dysfunctional Uterine Bleeding
- Secondary Amenorrhoea
- For diagnostic evaluation of endogenous estrogen status
- Secondary Amenorrhoea with adequate estrogen
- Secondary Amenorrhoea with inadequate estrogen
- Endometriosis
- Postponement of Menstruation

CONTRAINDICATION

Medroxyprogesterone Acetate (MPA) should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding
2. Known, suspected, or history of cancer of the breast
3. Known or suspected estrogen- or progesterone-dependent neoplasia
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions
5. Active or recent (within the past year) arterial thromboembolic disease (for example, stroke and myocardial infarction)
6. Known liver dysfunction or disease
7. Missed abortion
8. As a diagnostic test for pregnancy
9. Known hypersensitivity to the ingredients in Medroxyprogesterone Acetate (MPA) tablets
10. Known or suspected pregnancy.

WARNINGS AND PRECAUTIONS

1. Cardiovascular disorders.

An increased risk of stroke, deep vein thrombosis (DVT), pulmonary embolism, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these events occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history or family history of venous thromboembolism [VTE]), obesity, and systemic lupus erythematosus should be managed appropriately.

a. Stroke

In the estrogen plus progestin sub-study of the Women's Health Initiative (WHI) a statistically significant increased risk of stroke was reported in women receiving daily conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5mg) compared to women receiving placebo (31 versus 24 per 10,000 women-years). The increase in risk was reported after the first year and persisted.

b. Coronary heart disease

In the estrogen plus progestin substudy of WHI, no statistically significant increase of CHD events (defined as non-fatal myocardial infarction [MI], silent MI or CHD death was reported in

women receiving CE/MPA compared to women receiving placebo (39 versus 33 per 10,000 women-years). An increase in relative risk was reported in year one, and a trend toward decreasing relative risk was reported in years 2 through 5.
In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE 0.625 mg/ MPA 2.5mg per day reported no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/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 CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years.

c. Venous thromboembolism (VTE)
In the estrogen plus progestin substudy of WHI, a statistically significant two-fold greater rate of VTE, (DVT and pulmonary embolism [PE]), was reported in women receiving daily CE/MPA compared to women receiving placebo (35 versus 17 per 10,000 women years).
Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also reported.
The increase in VTE risk was reported during the first year and persisted.

2. Malignant neoplasms
a. Breast cancer
The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer in some studies. Observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. The risk increased with duration of use and appeared to return to baseline in about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen plus progestin combinations, doses, or routes of administration.

The WHI substudy reported an increased risk of breast cancer in women who took daily CE/MPA. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade, and hormone receptor status did not differ between the groups.
The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. **Endometrial cancer**
An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed

estrogen users is about 2- to 12 times greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.
Clinical surveillance of all women using estrogen plus progestin therapy is important.

Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

c. **Ovarian cancer**
The estrogen plus progestin substudy of WHI reported that daily CE/MPA increased the risk of ovarian cancer.

3. **Dementia**
In the estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to daily conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE/MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE/MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women.

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

PRECAUTIONS
A. General
1. Addition of a progestin when a woman has not had a hysterectomy:
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone.
Endometrial hyperplasia may be a precursor to endometrial cancer.
There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (lowering HDL, raising LDL) and impairment of glucose tolerance.

2. Undiagnosed abnormal vaginal bleeding:
In cases of undiagnosed abnormal vaginal bleeding, adequate diagnostic measures are indicated.
3. Elevated blood pressure:
Blood pressure should be monitored at regular intervals with estrogen plus progestin therapy.
4. Hypertriglyceridemia:
In patients with pre-existing hypertriglyceridemia, estrogen plus progestin therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.
5. Impaired liver function and past history of cholestatic jaundice:
Estrogens plus progestins may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.
6. Fluid Retention:
Progestins may cause some degree of fluid retention. Patients who have conditions which might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogen plus progestin are prescribed.
7. Hypocalcemia:
Estrogen plus progestin therapy should be used with caution in individuals with severe hypocalcemia.
8. Exacerbation of other conditions:

Estrogen plus progestin therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

DRUG INTERACTION
The following laboratory results may be altered by the use of estrogen plus progestin therapy:
1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and betathromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay, T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG) leading to increased circulating corticosteroid and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose metabolism.

ADVERSE EFECTS
The following adverse reactions have been reported in women taking progestins, including Medroxyprogesterone Acetate (MPA) tablets, without concomitant estrogens treatment:

1. Genitourinary system
Abnormal uterine bleeding (irregular, increase, decrease), change in menstrual flow, breakthrough bleeding, spotting, amenorrhea, changes in cervical erosion and cervical secretions.

2. Breasts
Breast tenderness, mastodynia or galactorrhea has been reported.

3. Cardiovascular
Thromboembolic disorders including thrombophlebitis and pulmonary embolism have been reported.

4. Gastrointestinal
Nausea, cholestatic jaundice

5. Skin
Sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash have occurred. Acne, alopecia and hirsutism have been reported.

6. Eyes
Neuro-ocular lesions, for example, retinal thrombosis, and optic neuritis.

7. Central nervous system
Mental depression, insomnia, somnolence, dizziness, headache, nervousness.

8. Miscellaneous
Hypersensitivity reactions (for example, anaphylaxis and anaphylactoid reactions, angioedema), rash (allergic) with and without pruritus, change in weight (increase or decrease), pyrexia, edema/fluid retention, fatigue, decreased glucose tolerance.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

1. Genitourinary system
Abnormal uterine bleeding/spotting, or flow; breakthrough bleeding; spotting; dysmenorrheal/pelvic pain; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts
Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

3. Cardiovascular
Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal
Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas.

5. Skin
Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

6. Eyes
Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system
Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

8. Miscellaneous
Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaplylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE
Overdosage of estrogen plus progestin therapy may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of CE/MPA together with institution of appropriate symptomatic care.

DOSAGES AND ADMINISTRATION
a) Dysfunctional Uterine Bleeding: For heavy bleeding:
• Deviry 10 mg 1 tid for the first 7 days followed by 1 bid for the next 7 days followed by 1 OD for the next 7 days.
• Deviry 10 mg 1 OD should be prescribed from 16th to 25th day in the next 2 cycles. In mild to moderate bleeding:
• Deviry 10 mg 1 OD from 1st to 14th day of the first cycle followed by Deviry 10 mg 1 OD from 16th to 25th day in the next 2 cycles.

b) Secondary Amenorrhoea For diagnostic evaluation of endogenous estrogen status:

• Deviry 10 mg 2 times daily for 5 days. Withdrawal bleeding indicates adequate estrogenisation.
Secondary Amenorrhoea with adequate estrogen:
• Deviry 10 mg cyclically from days 16 through 25 for six months; then stopped and the patient re-evaluated. Secondary Amenorrhoea with inadequate estrogen:
• Conjugase (Conjugated estrogens 0.625 mg) on days 1 through 25 and Deviry 10 mg on days 16 through 25 followed by five days no medication. Treatment should be continued for 4-6 months.
c) Endometriosis:
• Deviry 10 mg 1 tab to upto 5 tabs daily for 3-4 months followed by clinical evaluation. If necessary to continue for further 3 months.
d) Postponement of Menstruation:
• Treatment to be started 7 days before the anticipated date of menses. Deviry 10 mg daily till the postponement is desired. Higher dose required if treatment is started less than 7 days before the anticipated date of menses.

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

Pregnancy

Pregnancy Category X: Medroxyprogesterone Acetate (MPA) should not be used during pregnancy.
There may be increased risks for hypospadias, clitoral enlargement and labial fusion in children whose mothers are exposed to Medroxyprogesterone Acetate (MPA) during the first trimester of pregnancy. However, a clear association between these conditions with use of Medroxyprogesterone Acetate (MPA) has not been reported.

Nursing Mothers

Medroxyprogesterone Acetate (MPA) should not be used during lactation. Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins.

Pediatric Use

Medroxyprogesterone Acetate (MPA) is not intended for pediatric use and no clinical data has been reported in children.

Geriatric Use

Of the total number of subjects in the estrogen plus progestin substudy of the Women's Health Initiative (WHI), 44 percent (n = 7,320) were 65 years and older, while 6.6 percent (n = 1,095) were 75 years and older. In women 75 and older compared to women less than 75 years of age, there was a higher relative risk of non-fatal stroke and invasive breast cancer in the estrogen plus progestin group versus placebo. In women greater than 75 years of age, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen plus progestin group compared to placebo was 75 versus 24 per 10,000 women-years and 52 versus 12 per 10,000 women-years, respectively.

In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95 percent CI, 1.21-3.48). The

absolute risk of developing probable dementia with CE/MPA was 45 versus 22 cases per 10,000 women-years compared with placebo.

Eighty-two percent of the cases of probable dementia occurred in women that were older than 70 in the CE/MPA group. The most common classification of probable dementia in the estrogen plus progestin and placebo groups was Alzheimer's disease.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term intramuscular administration of Medroxyprogesterone Acetate (MPA) has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of Medroxyprogesterone Acetate (MPA) to rats and mice.

Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

Long-term continuous administration of estrogen plus progestin therapy, has shown an increased risk of breast cancer and ovarian cancer.

EXPIRY DATE

Three years from the date of manufacturing.

STORAGE

Store at temperature not exceeding 30°C. Protect from moisture.

PRESENTATION

Blister pack of 10 Tablets

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
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