PREMONOR

Tablets

Composition
Each tablet contains Norethisterone Acetate 5 mg

Action
Norethisterone is a strong progestogen with negligible androgenic effects. Complete transformation of the endometrium from a proliferative to a secretory state can be achieved in estrogen-primed women with orally administered doses of 100 -150 mg norethisterone per cycle.

The progestogenic effect of norethisterone on the endometrium is the basis of the treatment of dysfunctional bleeding, primary and secondary amenorrhea, and endometriosis with Premonor.

Gonadotropin secretion inhibition and an ovulation can be achieved with daily intake of 0.5 mg of norethisterone. Positive effects of Premonor on premenstrual symptoms can be traced back to suppression of ovarian function.
Due to the stabilizing effects of norethisterone on the endometrium, administration of Premonor can be used to shift the timing of menstruation.
Like progesterone, the thermogenic action of norethisterone alters the basal body temperature.

Pharmacokinetics
Absorption
Orally administered norethisterone is rapidly and completely absorbed over a wide dose range. Peak serum concentrations of about 16 ng/ml are reached within about 1.5 hours of administration of one tablet Premonor. Due to a marked first-pass effect, the bioavailability of norethisterone after an oral dose is about 64%.

Distribution
Norethisterone is bound to serum albumin and to sex hormone binding globulin (SHBG). Only about 3-4% of the total serum drug concentrations are present as free steroid, about 35% and 61% are bound to SHBG and albumin, respectively.

Norethisterone is transferred into milk and the drug levels in breast milk were found to be about 10% of those found in maternal plasma, irrespective of the route of administration. Based on a mean maximum drug level in maternal serum of about 16 ng/ml and an estimated daily intake of 600 ml of milk by the nursed infant, a maximum of about 1 mcg (0.02% of the maternal dose) could reach the infant.

Metabolism
Norethisterone is mainly metabolised by saturation of the double bond in ring A and the reduction of the 3-keto group to a hydroxyl group followed by a conjugation to the corresponding sulphates and glucuronides. Some of these metabolites are eliminated rather slowly from plasma, with half-lives of about 67 hours.
Therefore, during long-term treatment with daily oral administration of norethisterone, some of these metabolites accumulate in the plasma. Transformation of norethisterone to ethinylestradiol in vivo has been reported for many years but has not been determined quantitatively.

Elimination
Norethisterone is not excreted unchanged to a significant extent. Predominantly A-ring-reduced and hydroxylated metabolites as well as their conjugates (glucuronides and sulphates) are excreted via urine and feces in a ratio of about 7:3. The bulk of renally excreted metabolites were eliminated within 24 hours with a half-life of about 19 hours.

Indications
Premonor is indicated in amenorrhea; in abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer, and in endometriosis.

Contraindications

- Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a history of these conditions.
- Known or suspected carcinoma of the breast.
- Undiagnosed vaginal bleeding.
- Missed abortion.
- As a diagnostic test for pregnancy.
- Impaired liver function and liver disease.

Warnings

Discontinue medication-pending examination if there is a 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.

Detectable amounts of progestogens have been identified in the milk of mothers receiving them. The effect of this on the nursing infant has not been determined. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease.
Masculinization of the female fetus has occurred when progestogens have been used in pregnant women.

Pregnancy
Category X
THE USE OF NORETHISTERONE ACETATE DURING THE FIRST FOUR MONTHS OF PREGNANCY IS NOT RECOMMENDED.
Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no adequate evidence that such use is effective when such drugs are given during the first four months of pregnancy.
Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.

Adverse Reactions

The following adverse reactions have been observed in women taking Progestogens:

- Breakthrough bleeding, Spotting, Change in menstrual flow, Amenorrhea, Edema, Changes in weight (increase or decrease), Changes in cervical erosion and cervical secretions, Cholestatic jaundice, Rash (allergic) with and without pruritus, Melasma or chloasma, Mental depression.
- A statistically significant association has been demonstrated between use of estrogen-progestogen combination drugs and the following serious adverse reactions: thrombophlebitis; pulmonary embolism and cerebral thrombosis and embolism. For this reason, patients on progestogen therapy should be carefully observed.
- Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.
- The following adverse reactions have been observed in patients receiving estrogen-progestogen combination drugs: Rise in blood pressure in susceptible individuals, Premenstrual-like syndrome, Changes in libido, Changes in appetite, Cystitis-like syndrome, Headache, Nervousness, Dizziness, Fatigue, Backache Hirsutism, Loss of scalp hair, Erythema multiforme, Erythema nodosum, Hemorrhagic eruption , Itching.

Precautions

General

The pretreatment physical examination should include special reference to breasts and pelvic organs, as well as a Papanicolaou smear.
Because this drug may cause some degree of fluid retention, conditions that might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In cases of breakthrough bleeding, as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.
Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Any possible influence of prolonged progestogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine functions awaits further study.
A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestogen combination drugs. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric. The pathologist should be advised of progestogen therapy when relevant specimens are submitted.

Concomitant Estrogen Use
Studies of the addition of a progestin product to an estrogen replacement regimen for seven or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10 to 13 days of a progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks that may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The dosage used may be important in minimizing these adverse effects.

Laboratory Tests
The following laboratory result may be altered by the use of progestogens: Pregnanediol determination.
In addition, the following laboratory results may be altered by the concomitant use of estrogens with progestogens:

- Hepatic function
- Coagulation tests; increase in prothrombin, Factors VII, VIII, IX, and X
- Increase in PBI, BEI and a decrease in T3 uptake
- Metyrapone test reduce response

Nursing Mothers
Detectable amounts of progestogens have been identified in the milk of mothers receiving them. Because of the potential for serious adverse reactions in nursing infants from Norethisterone Acetate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions
Drug interactions that result in an increased clearance of sex hormones can lead to decreased therapeutic efficacy. This has been established with many hepatic enzyme-inducing drugs (including phenytoin, barbiturates, primidone, carbamazepine, and rifampicin); griseofulvin, oxcarbazepine, and rifabutin are also suspected.

Dosage and Administration

Therapy with Premonor must be adapted to the specific indications and therapeutic response of the individual patient.
This dosage schedule assumes the interval between menses to be 28 days.

Amenorrhea, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology: 2.5 to 10 mg Norethisterone Acetate starting with the fifth day of the menstrual cycle and ending on the 25th day.

Endometriosis
Initial daily dose of 5 mg Premonor for two weeks with increments of 2.5 mg per day of Premonor every two weeks until 15 mg per day of Premonor is reached. Therapy may be held at this level for from six to nine months or until annoying breakthrough bleeding demands temporary termination.

Progestin withdrawal bleeding usually occurs within 3-7 days after discontinuing Norethisterone therapy.
Patients with a part history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with Premonor

Presentation
Box of 20 tablets