Menoral®

Norethisterone EP Tablet

COMPOSITION

Menoral® Tablet: Each tablet contains Norethisterone EP 5 mg.

PHARMACOLOGY

Pharmacodynamics

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 effects of norethisterone on the endometrium are the basis of the treatment of dysfunctional bleeding, primary and secondary amenorrhea, and endometriosis with **Menoral®**. Gonadotropin secretion inhibition and anovulation can be achieved with daily intake of 0.5 mg of norethisterone. Positive effects of **Menoral®** on premenstrual symptoms can be traced back to suppression of ovarian function.

Due to the stabilizing effects of norethisterone on the endometrium, administration of **Menoral®** 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 **Menoral®**. 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 600ml of milk by the nursed infant, a maximum of about 1mcg (0.02% of the maternal dose) could reach the infant.

Metabolism: Norethisterone is mainly metabolized 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. Recent investigations have confirmed that norethisterone is partly metabolized to ethinylestradiol. Per one milligram of orally administered norethisterone, ethinylestradiol is formed equivalent to an oral dose of approximately 4 mcg in humans. Since the estrogenicity of norethisterone has always been assumed and experienced in clinical practice, the recent discovery of its metabolic characteristics does not change the existing recommendations for use.

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

Steady state conditions: During multiple-dose daily administration with norethisterone, an accumulation of the drug is unlikely because of the relatively short half-life of the drug. If, however, SHBG-inducing agents such as ethinylestradiol are co-administered, an increase in norethisterone serum levels can occur because of the binding of norethisterone to SHBG.

INDICATIONS

* Dysfunctional uterine bleeding (DUB) * Premenstrual syndrome (PMS), Mastopathy * Timing of menstruation * Endometriosis * Menorrhagia

DOSAGE AND ADMINISTRATION

Before starting **Menoral®**, a thorough general medical and gynecological examination (including the breasts and a cytological smear of the cervix) guided by the contraindications and warnings should be carried out and pregnancy must be excluded. As a precaution, control examinations should be conducted at intervals of about 6 months during long-term treatment with **Menoral®**. The tablets are to be swallowed whole with some liquid.

The efficacy of **Menoral®** could be reduced if the user forgets to take a tablet as directed. The woman should take only the last missed tablet as soon as she remembers and then continue tablet intake at her usual time on the next day.

If contraceptive protection is required, additional non-hormonal contraceptive methods should be used.

The following dosages are recommended:

1. Dysfunctional uterine bleeding (DUB)

The administration of 1 tablet **Menoral®** three times daily over 10 days usually leads to the arrest of uterine bleeding not associated with organic lesions within 1 - 3 days. Nevertheless, to ensure treatment success **Menoral®** must be taken for the full 10 days. About 2 to 4 days after completion of the treatment, withdrawal bleeding will occur with the intensity and duration of normal menstruation.

Occasionally, slight bleeding may occur after the initial arrest of bleeding. In these cases tablet taking must not be interrupted or stopped.

Missing arrest of haemorrhage, heavy break-through bleeding

If the vaginal bleeding does not stop despite correct tablet intake, an organic cause or an extra-genital factor (e.g. polyps, high-situated carcinoma of the cervix uteri or endometrium, myoma, residual of abortion, extra-uterine pregnancy, or coagulation disorders) must be considered so that other measures are then mostly required. This applies also in cases where after initial arrest of haemorrhage, fairly heavy bleeding still occurs during tablet taking.

Prophylaxis against recurrence of dysfunctional bleeding

To prevent recurrence of dysfunctional bleeding in patients with anovulatory cycles, it is recommended to administer **Menoral®** prophylactically.

1 tablet 1 to 2 times daily from the 16th to the 25th day of the cycle (1st day of the cycle = 1st day of the last bleeding). Withdrawal bleeding occurs a few days after administration of the last tablet.

2. Premenstrual syndrome (PMS), mastopathy

Premenstrual symptoms such as headaches, depressive moods, water retention, a feeling of tension in the breasts may be relieved or alleviated by one tablet **Menoral®** 1 - 3 times daily during the luteal phase of the cycle.

3. Timing of menstruation

Monthly menstrual bleeding can be postponed with administration of **Menoral®**. However, this method should be restricted to users who are not at risk of pregnancy during the treatment cycle.

Dosage: 1 tablet **Menoral®** 2 to 3 times daily for not longer than 10 - 14 days, beginning about 3 days before the expected menstruation. Bleeding will occur 2 - 3 days after medication has been stopped.

4. Endometriosis

Treatment should begin between the first and fifth day of the cycle with 1 tablet **Menoral®** twice daily, increasing to 2 tablets twice daily in the event of spotting. If, the bleeding ceases, the initial dose can be resumed. Duration of treatment is for at least 4 - 6 months. With uninterrupted daily intake, ovulation and menstruation do not usually occur. After discontinuation of hormone treatment withdrawal bleeding will occur.

5. Menorrhagia (hypermenorrhea)

Treatment with **Menoral®** 1 tablet 3 times daily from day 5-25 of the cycle has been shown to be effective in reducing menstrual blood loss.

CONTRAINDICATIONS

Norethisterone should not be used in the presence of the conditions listed below, which are derived also from information on other progestogen-only products. Should any of the conditions appear during the use of Norethisterone, the use of the preparation must be discontinued immediately.

* Known or suspected pregnancy
* Lactation
* Thromboembolic processes
* Diabetes mellitus with vascular involvement
* Presence or history of severe hepatic disease as long as liver function values have returned to normal
* Presence or history of liver tumors (benign or malignant)
* Known or suspected sex-hormone dependent malignancies
* Hypersensitivity to the active substances or to any of the excipients

WARNINGS AND PRECAUTIONS

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before Norethisterone is started or continued.

Circulatory disorders: It has been concluded from epidemiological surveys that the use of oral estrogen/progestogen containing ovulation inhibitors is attended by an increased incidence of thromboembolic diseases. Therefore, one should keep the possibility of an increased thromboembolic risk in mind, particularly when there is a history of thromboembolic disease.

Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilization, major surgery or major trauma. The increased risk of thromboembolism in the puerperium must be considered.

Treatment should be stopped at once if there are any symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumors: In rare cases, benign liver tumors, even more rarely, malignant liver tumors have been reported in users of hormonal substances such as the one contained in norethisterone. In isolated cases, these tumors have led to leading life-threatening intra-abdominal haemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking Norethisterone.

Other: Strict medical supervision is necessary if the patient suffers from diabetes.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarium. Women with a tendency to chloasma should avoid exposure to the sun or ultra violet radiation when taking Norethisterone.

Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Norethisterone also has estrogenic properties due to its partial conversion to estrogen estradiol. There are no corresponding estrogen related safety relevant findings available.

Reasons for immediate discontinuation of the tablets: Occurrence for the first time of migrainous headaches or more frequent occurrence of unusually severe headaches, sudden perceptual disorders (e.g. disturbances of vision or hearing), first signs of thrombophlebitis or thromboembolic symptoms (for example, unusual pains in or swelling of the legs, stabbing pains on breathing or coughing for no apparent reason), a feeling of pain and tightness in the chest, pending operations (six weeks beforehand), immobilization (for instance, following accidents), onset of jaundice, onset of anicteric hepatitis, generalized pruritus, significant rise in blood pressure, pregnancy.

PREGNANCY AND LACTATION

Use in Pregnancy: The use of Norethisterone during pregnancy is contraindicated. US FDA pregnancy category X.

Use in Lactation: **Menoral®** should not be used during lactation.

ADVERSE EFFECTS

Side effects more common during the first few months after starting Norethisterone include: visual disturbances, nausea, head aches, edema, migraine, dyspnea, hypersensitivity reactions (e.g. rash, urticaria) and in the indication of endometriosis changes in bleeding pattern (including irregular bleeding, scanty bleeding and amenorrhea). Other side effects including visual disturbances, nausea, headache, edema, migraine, dyspnea, hypersensitivity reactions (e.g. rash, urticaria) reported in Norethisterone users do not necessarily show a casual, relationship. Reference should also be made to the Warnings and Precautions section.

DRUG INTERACTIONS & OTHERS

Drug interactions which 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.

The use of progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

The requirement for oral anti-diabetics or insulin can change.

OVERDOSAGE

Acute toxicity studies performed with norethisterone acetate did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose.

STORAGE CONDITIONS

Store in a cool and dry place, protected from light and moisture. Keep out of reach of children.

HOW SUPPLIED

Menoral® Tablet: Each box contains 6 x10 tablets in blister pack.

Manufactured by

SQUARE
PHARMACEUTICALS LTD.
BANGLADESH