SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

PRIMOLUT N

Tablets

COMPOSITION

1 tablet contains norethisterone (17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one) 5,0 mg.

PHARMACOLOGICAL CLASSIFICATION

A. 21.8.2 Progesterones without estrogens.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Complete transformation of the endometrium can be achieved with 80 to 150 mg norethisterone, spread over 8 to 10 days, in adequately estrogen-primed castrated women. This amount is sufficient to bring the endometrium up to the condition which it is normally in at the end of the luteal phase. The menstruation-like withdrawal bleeding begins almost invariably 2 to 4 days after discontinuation of the medication.

Norethisterone has an inhibitory effect on the secretion of gonadotropins in the anterior lobe of the pituitary.

Norethisterone increases the basal body temperature: 10 mg norethisterone daily increases it by about 0,5°C.

In addition to the transformatory action norethisterone also has a styptic effect. A local influence on the endometrium leads to the cessation of dysfunctional bleeding.

Pharmacokinetic properties

Absorption

Orally administered norethisterone is 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 5 mg tablet Primolut N. 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 to 4% of the total serum drug concentration is present as free steroid, about 35% and 61% is bound to SHBG and albumin, respectively. The apparent volume of distribution of norethisterone is 4,4 $\pm$ 1,3 l/kg. Following oral administration, the drug serum level-time course follows a biphasic pattern. Both phases are characterised by half-lives of 1 to 2 and about 5 to 13 hours respectively.

Norethisterone is secreted into breast milk.

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 conjugation to the corresponding sulphates and glucuronides. Some of these metabolites are eliminated 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.

Norethisterone is partly metabolised to ethinylestradiol. Per one milligram of orally administered norethisterone, ethinylestradiol is formed equivalent to an oral dose of approximately 4 μg in humans.

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 faeces at a ratio of about 7:3.

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, relief of primary and secondary amenorrhoea, timing of menstruation, endometriosis.

CONTRA-INDICATIONS

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

- Known or suspected pregnancy.
- Lactation.
- Active thromboembolic processes or a history thereof.
- Diabetes mellitus with vascular involvement.
- Presence or history of severe hepatic disease, as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex hormone-dependent malignancies.
- Hypersensitivity to the active substance or to any of the excipients.

WARNINGS

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before Primolut N 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 arterial and venous thromboembolic diseases. Therefore one should keep the possibility of an increased thromboembolic risk in mind, particularly where there is a history of thromboembolic diseases.

Generally recognised risk factors for venous thromboembolism include a positive personal or family history (venous thromboembolism in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilisation, 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 symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumours

Benign liver tumours and malignant liver tumours have been reported in users of hormonal substances such as the one contained in Primolut N. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking Primolut N.

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 (eg 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), immobilisation (for instance, following accidents), onset of jaundice, onset of anicteric hepatitis, generalised pruritus, significant rise in blood pressure, pregnancy.

Other

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

DOSAGE AND DIRECTIONS FOR USE

Medical examination

A complete medical history should be taken and a physical and gynaecological examination should be performed prior to the initiation or reinstitution of the use of Primolut N, guided by the “Contra-indications” and “Warnings”, and these should be repeated during the use of Primolut N. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, and should also include cervical cytology.

The tablets are to be swallowed whole with some liquid.

Unless otherwise prescribed by the doctor, the following dosages are recommended.

Dysfunctional uterine bleeding

The administration of 1 tablet Primolut N 3 times daily over 10 days leads to the arrest of uterine bleeding not associated with organic lesions within 1 to 3 days. In individual cases, bleeding usually diminishes during the first few days after the commencement of tablet-taking and does not stop until about five days later. For the treatment to be successful, Primolut N administration should be continued regularly even after the arrest of bleeding (up to a total of 30 tablets).

About 2 to 4 days after discontinuation of treatment a withdrawal bleeding will occur resembling a normal menstruation in intensity and duration.

Slight bleeding during tablet-taking

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

Lack of arrest of haemorrhage, continuous or reoccurrence of bleeding

The use of Primolut N may assist in the differential diagnosis of uterine bleeding. If the bleeding does not stop in spite of regular tablet-taking, an organic cause must be considered. The attending physician must be informed immediately, because further measures are then mostly required. This also applies in cases where after initial arrest of haemorrhage, heavier bleedings still occur during tablet-taking.

Prevention of recurrence

To prevent the recurrence of dysfunctional bleeding, it is recommended to administer Primolut N prophylactically during the next three cycles, ie 1 tablet Primolut N 2 to 3 times daily from the 19th to the 26th day of the cycle (1st day of the cycle = 1st day of the last bleeding). The withdrawal bleeding occurs some days after administration of the last tablet.

Only the physician can decide whether this measure is necessary. The physician's decision is then based on the course of the basal body temperature, which must be measured daily.

Relief of primary and secondary amenorrhoea

In the case of secondary amenorrhoea hormone treatment is to be given at the earliest 8 weeks after the last menstrual period.

In order to induce a menstruation-like bleeding, an estrogen (eg estradiol valerate 10 mg) is to be given before the administration of Primolut N.

However, before treatment is commenced, the presence of a prolactin-producing pituitary tumour should be excluded because the possibility cannot be ruled out that macroadenomas increase in size when exposed to higher doses of estrogen for prolonged periods of time.

Commencement of treatment

2 ampoules estradiol valerate 10 mg IM on the 1st day of treatment and 1 ampoule of estradiol valerate 10 mg IM on the 14th day of treatment, followed by 1 tablet Primolut N 2 to 3 times daily from the 19th to the 26th day of treatment. Withdrawal bleeding starts on about the 28th day.

Continuation of treatment (over at least 2 to 3 cycles)

1 ampoule estradiol valerate 10 mg IM on the 6th and 16th days of the artificial cycle, followed by 1 tablet Primolut N twice daily from the 19th to the 26th day of the cycle (1st day of bleeding = 1st day of the cycle).

An attempt can then be made to stop the estrogen treatment and to induce a cyclical bleeding by the administration of 1 tablet Primolut N twice daily from the 19th to the 26th day of the cycle.

Exception: Patients of whom it can be safely assumed that endogenous estrogen production is insufficient (primary amenorrhoea in gonadal dysgenesia).

Please note

During treatment pregnancy must not occur. Contraception should be practised with non-hormonal methods (with the exception of the rhythm and temperature methods). If withdrawal bleeding at regular intervals of about 28 days fails to occur under the therapeutic scheme (see above), pregnancy must be considered despite the protective measures. The treatment must then be interrupted until the situation has been clarified by differential diagnosis.

Premenstrual syndrome, cyclical mastopathy

Premenstrual symptoms such as headaches, depressive moods, water retention, a feeling of tension in the breasts, may be relieved or palliated by 1 tablet Primolut N 2 to 3 times daily from the 19th to the 26th day of the cycle.

The remarks under "Please note" for the indication "Primary and secondary amenorrhoea" apply to this indication.

Timing of menstruation

The monthly bleeding can be brought forward or delayed if particular circumstances require this. However, bringing the withdrawal bleeding forward with progestogen-estrogen combinations is preferred, because the occurrence of a pregnancy is virtually ruled out by the inhibition of ovulation. As opposed to this, the postponement of menstruation calls for the use of Primolut N at a time when the necessary exclusion of pregnancy can be problematical since Primolut N must be given at a time when pregnancy cannot be excluded using the currently available examination methods. Therefore, this method remains restricted to those cases in which there is no possibility of early pregnancy in the cycle concerned.

Dosage: 1 tablet Primolut N 3 times daily for not longer than 10 to 14 days, beginning about 3 days before the expected menstruation. Bleeding will occur 2 to 3 days after having stopped medication. If it does not, the doctor must be consulted.

Endometriosis

Treatment is commenced on the 5th day of the cycle with 1 tablet Primolut N twice daily, increasing to 2 tablets twice daily in the event of spotting. When the bleeding ceases, the initial dose can be resumed. Duration of treatment: at least 4 to 6 months. During treatment, ovulation and menstruation do not occur. After discontinuation of hormone treatment a withdrawal bleeding will occur.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

Undesirable effects are more common during the first months after start of intake of Primolut N, and subside with duration of treatment. In addition to the adverse effects listed under “Special precautions”, the following undesirable effects have been reported in users of Primolut N, although a causal relationship could not always be confirmed.

In the indication of endometriosis, changes in bleeding pattern including irregular bleeding, scanty bleeding and amenorrhoea may occur.

Other side-effects that have been reported in users of Primolut N but for which the association has been neither conformed nor refuted are:

Organ system	
Eye disorders	Visual disturbances
Gastrointestinal disorders	Nausea
General disorders and administration site conditions	Headache, oedema
Nervous system disorders	Migraine
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Skin and subcutaneous tissue disorders	Hypersensitivity reactions (eg rash, urticaria)

Special precautions

Diabetes mellitus must be actively excluded as this disease requires careful supervision. The requirements for oral antidiabetics or insulin may change.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation when taking Primolut N.

Patients who have a history of psychic 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 the estrogen ethinylestradiol (see “Pharmacokinetic properties”). There were no corresponding estrogen-related safety relevant findings during the long period of post-marketing surveillance.

Interaction with other medicines and other forms of interaction

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.

Laboratory tests

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, eg 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.

Pregnancy and lactation

The use of Primolut N during pregnancy is contra-indicated.

Primolut N should not be used during lactation.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Treatment is supportive and symptomatic.

IDENTIFICATION

White, round tablet, biconvex, imprinted with "AN" in a regular hexagon on one side.

PRESENTATION

30 or 150 tablets in brown glass bottles with tamperproof closures made of polyethylene or in aluminium/PVC blisters.

STORAGE INSTRUCTIONS

Keep in well closed containers and protected from light. Store below 30°C. Keep out of reach of children.

REFERENCE NUMBER

G3124 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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