

PRIMOLUT N®

Norethisterone 5 mg tablets

Presentation

Each round, white, flat, 7 mm tablet is impressed with an "AN" in a regular hexagon on one side and quarter-scored on the other and contains 5 mg norethisterone.

Uses

Actions

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 oestrogen-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, and endometriosis with PRIMOLUT N.

Gonadotropin secretion inhibition and anovulation can be achieved with a daily intake of 0.5 mg of norethisterone. Positive effects of PRIMOLUT N on premenstrual symptoms can be traced back to suppression of ovarian function.

Due to the stabilising effects of norethisterone on the endometrium, administration of PRIMOLUT N 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 PRIMOLUT N tablet. 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 medicine concentrations are present as free steroid, about 35% and 61% are bound to SHBG and albumin, respectively. The apparent volume of distribution of norethisterone is 4.4 ± 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 - 2 and about 5 -13 hours, respectively.

Norethisterone is transferred into milk and the medicine 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 medicine 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 μ g (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 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.

- Norethisterone is partly metabolised to ethinyloestradiol after oral administration of norethisterone or norethisterone acetate in humans. This conversion results in an equivalent dose of about 4-6 μ g ethinyloestradiol per 1 mg orally administered norethisterone / norethisterone acetate.

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 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 medicine is unlikely because of the relatively short half-life of the medicine. If, however, SHBG-inducing agents such as ethinyloestradiol are co-administered, an increase in norethisterone serum levels can occur because of the binding of norethisterone to SHBG.

Indications

Dysfunctional bleeding, premenstrual syndrome, cyclical mastopathy, timing of menstruation, endometriosis, menorrhagia.

Dosage and Administration

The tablets are to be swallowed whole with some liquid.

The efficacy of PRIMOLUT N 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:

Dysfunctional uterine bleeding

The administration of one tablet PRIMOLUT N three times daily over 10 days, in the majority of cases, leads to the arrest of uterine bleeding that is not associated with organic lesions within 1 to 3 days. Nevertheless, to ensure treatment success, PRIMOLUT N 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.

- Slight bleeding during tablet-taking

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, carcinoma of the cervix uteri or endometrium, myoma, residua 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 re-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 PRIMOLUT N prophylactically. One 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.

Premenstrual syndrome, cyclical mastopathy

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

Timing of menstruation

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

Dosage: One tablet PRIMOLUT N 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.

Endometriosis

Treatment should begin between the first and fifth day of the cycle with one tablet PRIMOLUT N twice daily, increasing to two tablets twice daily in the event of spotting. If the bleeding ceases, dose reduction to the initial dose should be considered. Treatment is to be continued 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.

Menorrhagia (hypermenorrhoea)

Treatment with PRIMOLUT N one tablet 3 times daily from day 5 - 25 of the cycle has been shown to be effective in reducing menstrual blood loss.

Contraindications

PRIMOLUT N should not be used in the presence of the conditions listed below, which are derived also from information on progestogen-only products and combined oral contraceptives (COCs). 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
- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or a history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris)

- A high risk of venous or arterial thrombosis (see ‘Warnings and Precautions’)
- History of migraine with focal neurological symptoms.
- 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 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 PRIMOLUT N is started or continued.

- Circulatory disorders

It has been concluded from epidemiological surveys that the use of oral oestrogen/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 recognised 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 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 any symptoms of an arterial or venous thrombotic event or suspicion thereof.

- Tumours

In rare cases, benign liver tumours, and even more rarely, 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.

- Other

Strict medical supervision is necessary if the patient suffers from diabetes. The requirement for oral anti-diabetics or insulin can 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 ultra violet radiation when taking PRIMOLUT N.

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

Norethisterone also has oestrogenic properties due to its partial conversion to oestrogen, ethinyloestradiol. There were no corresponding oestrogen-related safety-relevant findings during the long period of post-marketing surveillance.

- **Medical Examination**

A complete medical history should be taken and a physical and gynaecological examination should be performed, including the exclusion of pregnancy, prior to the initiation or reinstatement of the use of PRIMOLUT N, guided by the “Contraindications” and “Warnings and Precautions” sections 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.

- **Reasons for immediate discontinuation of the tablets are:**

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); immobilisation (for instance, following accidents); onset of jaundice or generalised pruritus (or history of jaundice or severe pruritus during pregnancy); onset of anicteric hepatitis; significant rise in blood pressure; pregnancy.

Additional warnings based on the partial metabolisation of norethisterone to ethinyloestradiol

After oral administration, norethisterone is partly metabolised to ethinyloestradiol resulting in an equivalent dose of about 4-6 µg ethinyloestradiol per 1 mg orally administered norethisterone/norethisterone acetate (see ‘Pharmacokinetic properties’).

Due to the partial conversion of norethisterone to ethinyloestradiol, administration of PRIMOLUT N is expected to result in similar pharmacological effects as seen with COCs. Therefore the following general warnings associated with the use COCs should be considered in addition:

- **Circulatory disorders**

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large,

prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

Overall the risk for venous thromboembolism (VTE) in users of low oestrogen dose (< 50 µg ethinyloestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

VTE may be life-threatening or may have a fatal outcome (in 1-2 % of the cases).

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of deep venous thrombosis (DVT) can include: unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg which may be felt only when standing or walking, increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain, which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen.

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A COC should not be prescribed in case of a negative risk benefit assessment. (see section 'Contraindications')

The risk of venous or arterial thrombotic/ thromboembolic events or of a cerebrovascular accident increases with:

- Age
- Obesity (body mass index over 30 kg/m²)
- A positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation
- Smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- Dyslipoproteinemia
- Hypertension
- Migraine
- Valvular heart disease
- Atrial fibrillation

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C

(APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (<0.05 mg ethinylloestradiol).

- Tumours

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Malignancies may be life-threatening or may have a fatal outcome.

- Other

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare.

However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Crohn's disease and ulcerative colitis have been associated with COC use.

Pregnancy and Lactation

- Use in Pregnancy

The use of PRIMOLUT N during pregnancy is contraindicated.

Pregnancy (Category D): "Medicines which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details".

- Use in Lactation

PRIMOLUT N should not be used during lactation.

Preclinical Safety Data

Non-clinical data on norethisterone or its esters reveal no special risk for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential. However, it should be kept in mind that sexual steroids might stimulate the growth of hormone-dependent tissues and tumours.

Reproduction toxicity studies showed the risk of masculinisation in female foetuses when administered in high doses at the time of the development of the external genitalia. Since epidemiological studies show that this effect is relevant for humans after higher dosages, it is to be stated that PRIMOLUT N may provoke signs of virilisation in female foetuses if administered during the hormone-sensitive stage of somatic sexual differentiation (from day 45 of pregnancy onwards). Apart from this, no indications of teratogenic effects were obtained from the studies.

No studies to evaluate a possible sensitising potential of the medicine substance were performed.

Effects on ability to Drive and use Machines

Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

Adverse Effects

Adverse effects are more common during the first months after start of intake of PRIMOLUT N preparations and subside with duration of treatment. In addition to the adverse effects listed in the “Warnings and Precautions” section, the following undesirable effects have been reported in users of PRIMOLUT N preparations, although a causal relationship could not always be confirmed:

The table below reports adverse reactions by MedDRA system organ classes. The frequencies are based on reporting rates from post-marketing experience and literature.

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10 000 to < 1/1000	Very rare < 1/10 000
Immune system disorders				Hypersensitivity reactions	
Nervous system disorders		Headache	Migraine		
Eye disorders					Visual disturbances
Respiratory, thoracic and mediastinal disorders					Dyspnoea
Gastrointestinal disorders		Nausea			
Skin and subcutaneous tissue disorders				Urticaria Rash	
Reproductive system and breast disorders	Uterine/Vaginal bleeding including Spotting* Hypomenorrhoea*	Amenorrhoea*			
General disorders and administration site conditions		Oedema			

* in the indication of endometriosis

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Interactions

Medicine 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 medicines (including phenytoin, barbiturates, primidone, carbamazepine, rifampicin, oxcarbamazepine, St. John's Wort and rifabutin); griseofulvin is also suspected.

Progestogens may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may be affected (e.g. cyclosporin).

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

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, 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.

Overdosage

Acute toxicity studies in animals 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.

Pharmaceutical Precautions

Shelf life: 3 years

Special precautions for storage:
Blister packs, store at or below 30 °C

Medicine Classification

Prescription Medicine

Package Quantities

10 blister packs each containing 10 x 5 mg tablets.

Further Information

List of excipients

Lactose monohydrate, maize starch, magnesium stearate.

Nature and contents of container

PRIMOLUT N tablets are contained in blister packs consisting of transparent films made of polyvinyl chloride and metallic foils made of aluminium (mat side hot sealable).

Instructions for use/handling

Store all medicines properly and keep them out of reach of children.

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