

# PRIMOLUT N<sup>®</sup>

Norethisterone 5 mg tablets

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## Presentation

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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.

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## Uses

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### *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  $4.4 \pm 1.3$  L/kg. Following oral administration, the drug serum level time course follows a biphasic pattern. Both phases are characterised by half-lives of 1 - 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  $\mu$ 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.

Transformation of norethisterone to ethinyloestradiol *in vivo* has been reported for many years but has not been determined quantitatively. Recent investigations have confirmed that norethisterone is partly metabolised to ethinyloestradiol. Per one milligram of orally administered norethisterone, ethinyloestradiol is formed equivalent to an oral dose of approximately 4  $\mu$ g 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 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.

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## Dosage and Administration

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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 16<sup>th</sup> to the 25<sup>th</sup> day of the cycle (1<sup>st</sup> day of the cycle = 1<sup>st</sup> 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.

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## **Contraindications**

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PRIMOLUT N 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 PRIMOLUT N, the use of the preparation must be discontinued immediately.

- Known or suspected pregnancy
- Lactation
- Active venous thromboembolic disorders
- Arterial and cardiovascular disease present or in history (e.g. myocardial infarction, cerebrovascular accident, ischaemic heart disease)
- 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

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## Warnings and Precautions

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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.

### **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 fetuses 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.

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## Adverse Effects

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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			
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\* in the indication of endometriosis

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

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## Interactions

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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.

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## Overdosage

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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.

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## Pharmaceutical Precautions

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**Shelf life:** 3 years

**Special precautions for storage:**

Blister packs, store at or below 30 °C

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## **Medicine Classification**

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Prescription Medicine

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## **Package Quantities**

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10 blister packs each containing 10 x 5 mg tablets.

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## **Further Information**

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**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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## **Name and Address**

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## **Date of Preparation**

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24 March 2009