

## PRODUCT INFORMATION

### PRIMOLUT® N

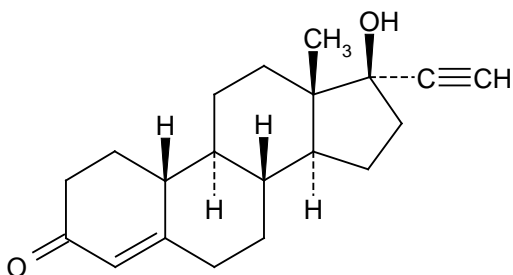
#### NAME OF THE MEDICINE

Primolut N

Each tablet of Primolut N contains 5 mg norethisterone.

Norethisterone is 17  $\beta$ -Hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one

CAS 68-22-4



C<sub>20</sub>H<sub>26</sub>O<sub>2</sub> MW=298.4

#### DESCRIPTION

Norethisterone is a white or yellowish-white odourless crystalline powder. It is practically insoluble in water; slightly to sparingly soluble in alcohol; soluble in chloroform and in dioxan; slightly soluble in ether.

Primolut N also contains the inactive excipients lactose, maize starch, magnesium stearate.

#### PHARMACOLOGY

##### Pharmacological actions

Norethisterone is a progestogen with negligible androgenic effects. Complete transformation of the endometrium from a proliferative to a secretory state was achieved in oestrogen-primed castrated or climacteric women who were administered oral doses of 100-150 mg norethisterone per cycle. The progestogenic effects of norethisterone on the endometrium is the basis of the treatment of dysfunctional bleeding, primary and secondary amenorrhea, 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, norethisterone is thermogenic and alters the basal body temperature.

## Pharmacokinetics

- Absorption

In a single oral dose pharmacokinetic study in 24 healthy postmenopausal women different progesterone preparations were studied. Peak serum concentration after administration of 5mg Primolut N were  $16 \pm 5$  ng/mL;  $t_{\max}$  was  $1.5 \pm 0.6$  hours. In a study of 6 women aged 21-23 years, the bioavailability of a single dose of 1 mg norethisterone compared to an equivalent intravenous dose ranged from 47% to 73%, suggesting a significant first pass effect. This study showed that the disposition of norethisterone follows a biexponential pattern with half lives of 0.4-2.6 and 5-13 hours respectively. The apparent volume of disposition was  $4.28 \pm 0.56$  L/kg.

- 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. 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 drug levels in breast milk were found to be about 10% of those found in maternal plasma.

- 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 sulfates and glucuronides. Some of these metabolites are eliminated slowly from plasma, building approximately to a peak at the midpoint of the treatment cycle and rapidly dropping to near baseline levels when treatment is stopped. Norethisterone is partly metabolised to ethinyloestradiol after oral administration of norethisterone in humans. This conversion results in an equivalent dose of about 4 µg ethinyloestradiol per 1 mg orally administered norethisterone.

- Excretion

Norethisterone is not excreted unchanged to a significant extent. Predominantly A-ring-reduced and hydroxylated metabolites as well as their conjugates (glucuronides and sulfates) are excreted via urine and feces. In a study of radiolabelled norethisterone in 7

women, 37.4% to 80% of the orally administered dose was excreted in the urine over 5 days 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 ethinyloestradiol are co-administered, an increase in norethisterone serum levels can occur because of the binding of norethisterone to SHBG.

## **INDICATIONS**

Dysfunctional bleeding, primary and secondary amenorrhoea, premenstrual syndrome, delay of menstrual period, endometriosis, adjunct to oestrogen hormone replacement therapy.

## **CONTRAINDICATIONS**

Primolut N should not be used in the presence of any 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 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.
- Dubin-Johnson syndrome
- Rotor syndrome
- Missed abortion
- Undiagnosed vaginal or urinary bleeding
- Undiagnosed breast pathology

## **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 where there is a history of thromboembolic diseases.

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 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.

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.

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Nonfunctional causes should also be borne in mind, and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when

treating all patients and 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.

Weight gain may be associated with the use of the medication. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

Primolut N tablets are not to be used as a test for pregnancy or where pregnancy is suspected.

In perimenopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of hormone replacement therapy (HRT). An endometrial biopsy may be performed at the discretion of the attending doctor.

Additional Precautions applicable to other progestogen products may also apply.

- Medical examination

A complete medical history should be taken and a physical and gynaecological examination should be performed prior to the initiation or reinstatement of the use of Primolut N, guided by the Contraindications and Precautions, 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.

#### **Additional warnings based on the partial metabolism of norethisterone to ethinyloestradiol**

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 (see Pharmacokinetics). Therefore the following general warnings associated with the use of COCs should be considered in addition, when assessing the individual risk benefit for using Primolut N.

- Circulatory disorders

The risk of venous thromboembolism (VTE) is highest during the first year of use of a COC. This increased risk is present after initially starting, 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 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).

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 venous (includes pulmonary embolism (PE) and deep venous thrombosis (DVT) or arterial thrombotic/thromboembolic (includes myocardial infarction (MI), vascular occlusion and cerebrovascular accident) events can include: unilateral leg pain and/or swelling; 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; sudden severe pain in the chest which may increase with deep breathing; 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; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe, prolonged headache with no known cause; sudden partial or complete loss of vision; diplopia; sense of anxiety; dizziness; slurred speech or aphasia; sudden confusion; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

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).

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. Primolut N should not be prescribed in case of a negative risk benefit assessment (see 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/m<sup>2</sup>)
- 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 treatment

- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue treatment (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)
- Dyslipoproteinaemia
- Hypertension
- Migraine
- Valvular heart disease
- Atrial fibrillation

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

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 treatment (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the medicine.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

- 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 (see **Carcinogenicity**).

- Other

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

If sustained clinically significant hypertension develops during the treatment then it is prudent for the physician to withdraw the medicine and treat the hypertension. Where considered appropriate, treatment 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 or Primolut N use is currently inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic 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 treatment 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 treatment.

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

**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, onset of anicteric hepatitis, generalised pruritus, significant rise in blood pressure, pregnancy.

**Use in Pregnancy – Category D\***

The use of Primolut N during pregnancy is contraindicated.

Studies on reproduction toxicology performed with norethisterone acetate as well as norethisterone enantate led to signs 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 high dosages, it is to be stated that Primolut N may provoke signs of virilisation in female fetuses if administered during the hormone-sensitive stage of somatic sexual differentiation (from

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\*Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.



day 45 of pregnancy onwards). Apart from this, no indications of teratogenic effects were obtained from the studies.

In animal studies, maternal administration of high doses of synthetic oestrogens produced urogenital malformations in the offspring.

### **Use in Lactation**

Primolut N should not be used during lactation.

### **Paediatric Use**

Primolut N is only indicated after menarche.

### **Genotoxicity**

The genotoxic potential of norethisterone has not been fully investigated, although it was shown to be negative in the Ames test for reverse gene mutations and in assays for DNA adduct formation and unscheduled DNA synthesis.

There is limited evidence available in the literature suggesting that oestrogens may be weakly genotoxic at high doses. Ethinyloestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells *in vitro*) and gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high concentrations). *In vivo* studies did not confirm these results.

### **Carcinogenicity**

No study has been conducted to examine the carcinogenicity of Primolut N.

Benign hepatic adenomas have been found to be associated with the use of oral contraceptives containing sex hormones such as norethisterone. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage.

It must also be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care (also see PRECAUTIONS)

Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver. The clinical relevance of these findings is uncertain.

### **Effect on 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.

## INTERACTIONS WITH OTHER MEDICINES

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, St. John's Wort and rifampicin); griseofulvin, oxcarbazepine, and rifabutin are also suspected. Progestogens may interfere with the metabolism of other drugs. 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.

## ADVERSE 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 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 confirmed 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	rash, urticaria
Immune system disorders	hypersensitivity reactions

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens:

*Hypersensitivity:* Anaphylaxis and anaphylactoid-like reactions.

*Thromboembolic disease:* Thrombophlebitis and pulmonary embolism

*Central nervous system:* Nervousness, insomnia, somnolence, fatigue, depression, dizziness and tremor. Some patients may complain of pre-menstrual type depression.

*Dermatological:* Urticaria, pruritus, rash, acne, hirsutism, alopecia and sweating.

*Genitourinary:* Irregular uterine bleeding, spotting and amenorrhoea

*Breast:* Tenderness and galactorrhoea

*Cervix:* Changes in excretions and secretions.

*Other:* Hyperpyrexia, Cushing's syndrome, weight gain. Moderate elevation of blood pressure, transient elevation of alkaline phosphatase and/or serum transaminase

activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts.

## **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.

- **Dysfunctional bleeding**

Primolut N 1 tablet is to be taken 3 times daily for 10 days. In the majority of cases this will arrest 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.

Occasionally, slight bleeding may occur after the initial suspension of bleeding. Also in these cases tablet intake should not be interrupted or stopped.

If 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 also applies to cases where after an initial suspension of bleeding, fairly heavy bleeding reoccurs during tablet intake.

To prevent dysfunctional bleeding recurrence in patients with anovulatory cycles Primolut N can be administered 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 the last tablet intake.

- **Primary and secondary amenorrhoea**

Hormone treatment of secondary amenorrhoea can be carried out only after the exclusion of pregnancy. Before treatment of primary or secondary amenorrhoea is commenced the presence of a prolactin-producing pituitary tumour should be excluded. The possibility cannot be ruled out that macroadenomas increase in size when exposed to high doses of oestrogen for prolonged periods of time.

Endometrial priming with an oestrogen must be carried out (e.g., for 14 days) before beginning treatment with Primolut N. Thereafter 1 tablet of Primolut N is given 1 to 2 times daily for 10 days. Withdrawal bleeding occurs within a few days after intake of the last tablet.

In patients in whom sufficient endogenous oestrogen production has been achieved, an attempt can be made to stop the oestrogen treatment and to induce cyclical bleeding by administering 1 tablet of Primolut N twice daily from the 16th to the 25th day of the cycle.

- **Premenstrual syndrome**

One tablet of Primolut N taken 1 to 3 times daily during the luteal phase of the cycle may relieve or improve premenstrual symptoms such as headaches, depressive moods, water retention, and a feeling of tension in the breasts.

- **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: 1 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 having stopped medication.

- **Endometriosis**

Treatment should begin between the first and 5th day of the cycle with 1 tablet Primolut N twice daily. In the event of spotting, the dose can be increased to 2 tablets twice daily. If bleeding ceases, dose reduction to the initial dose should be considered. Treatment is to be continued for at least 4 to 6 months. With uninterrupted daily intake, ovulation and menstruation do not usually occur. After discontinuation of hormone treatment withdrawal bleeding will occur.

## **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.

For information on the management of overdose, contact Poisons Information Centre 131126.

## **PRESENTATION AND STORAGE CONDITIONS**

Each Primolut N tablet consists of 5 mg of norethisterone. Tablets are round and white, quarter scored on one side, with the letters 'AN' in a regular hexagon on the other side.

Primolut N tablets come in blister packs, in quantities of 30 or 100 tablets.

Not all pack sizes may be marketed.

Store below 30°C.

**NAME AND ADDRESS OF THE SPONSOR**

Bayer Australia Ltd  
ABN 22 000 138 714  
875 Pacific Highway  
Pymble NSW 2073  
Australia

**POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE, S4

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

19 August 1991

**DATE OF MOST RECENT AMENDMENT**

28 July 2016

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