SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

PRIMOLUT N 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains norethisterone 5 mg.

Excipient with known effect
Lactose

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dysfunctional uterine bleeding, relief of primary and secondary amenorrhoea, timing of menstruation, endometriosis.

4.2 Posology and method of administration

Posology

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, but she must not take a double dose.

If contraception protection is required, additional non-hormonal (barrier) contraceptive methods should be used.

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, 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 or an extragenital factor (e.g. polyps, carcinoma of the cervix uteri or endometrium, myoma, residua of abortion, extra-uterine pregnancy, or coagulation disorders) 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 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). The withdrawal bleeding occurs a few 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

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 higher doses of estrogen for prolonged periods of time.

Endometrial priming with an estrogen 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 estrogen production has been achieved, an attempt can 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 16th to the 25th day of the cycle.

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

<u>Please note</u>

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

1 tablet 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 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.

Method of administration

The tablets are to be swallowed whole with some liquid.

4.3 Contraindications

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 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.

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 of a history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- A high risk of venous or arterial thrombosis (see section 4.4).
- 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.
- Use of direct-acting antiviral (DAA) medicines containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these (see section 4.5).
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex hormone-dependent malignancies.

4.4 Special warnings and precautions for use

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 (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 (see section 4.6).

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.

Other

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

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 medicine discontinued if the depression recurs to a serious degree.

Depressed mood, depression and risk of suicidality

Depressed mood and depression are well-known undesirable effects of hormonal containing products. Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

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 contraindications (see section 4.3) and warnings (see section 4.4), 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.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Additional warnings based on the partial metabolism of norethisterone to ethinylestradiol

After oral administration, norethisterone is partly metabolised to ethinylestradiol resulting in an equivalent dose of about 4 to 6 µg ethinylestradiol per 1 mg orally administered norethisterone/ norethisterone acetate (see section 5.2).

Due to partial conversion of norethisterone to ethinylestradiol, 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 of COCs should be considered:

Circulatory disorders (thromboembolic events)

The risk of venous thromboembolic events is highest during the first year of use. This increased risk is present after initially starting a combined oral contraceptive (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 estrogen dose (< 50 µg ethinylestradiol) 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 to 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.

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 immobilization, 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 remobilization
- 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, hyperhomocysteinaemia, 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 COC use (< 0,05 mg ethinylestradiol).

Tumours

Cervical Cancer
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.

Breast Cancer
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 conditions

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

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 (SLE); haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens 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.

4.5 Interaction with other medicines and other forms of interactions

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

Effects of other medicines on PRIMOLUT N
Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of sex hormones and which may lead to changes in the uterine bleeding profile and/or reduction of the therapeutic effect.

Enzyme induction can be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of medicine therapy enzyme induction may be sustained for about 4 weeks.

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme induction), e.g.:
Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, rifabutin and products containing St. John's wort.

Substances with variable effects on the clearance of sex hormones, e.g.:
When co-administered with sex hormones, many HIV/HCV protease inhibitors and nonnucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of sex hormones (enzyme inhibitors):
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen, or the progestin, or both.
Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1,4 to 1,6-fold, respectively when taken concomitantly with a combined hormonal medicine containing 0,035 mg ethinylestradiol.

Effects of PRIMOLUT N on other medicines
Progestogens may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).
In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism-based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a minor increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase slightly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

Pharmacodynamic interactions
Co-administration of ethinylestradiol-containing medicines with direct-acting antiviral (DAA) medicines containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in ALT levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see section 4.3).

Other forms of interaction

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.

4.6 Pregnancy and lactation

Pregnancy
The use of PRIMOLUT N during pregnancy is contraindicated.

Lactation
PRIMOLUT N should not be used during lactation. Norethisterone is secreted into breast milk (see section 5.2).

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable 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 undesirable effects listed in section 4.4, the following undesirable effects have been reported in users of PRIMOLUT N, although a causal relationship could not always be confirmed.

System Organ Class (MedDRA)	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1 000 to < 1/100)	Rare (≥ 1/10 000 to < 1/1 000)	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 Endometriosis

Post-marketing side effects

Depression can be severe and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact that medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There have been no reports of ill-effects from overdosage and treatment is generally unnecessary. There are no special antidotes, and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system;
Progestogens, Estren derivatives
ATC Code: G03DC02

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.

5.2 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 ± 1,3 l/kg.

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 600 ml of milk by the nursed infant, a maximum of about 1 µg (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 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 mainly metabolised to ethinylestradiol after oral administration of norethisterone or norethisterone acetate in humans. This conversion results in an equivalent dose of about 4-6 µg ethinylestradiol per 1 mg orally administered norethisterone/norethisterone acetate.

Elimination

Plasma clearance for norethisterone is approximately 0,7 l/hr/kg. Norethisterone is excreted in both urine and faeces, primarily as metabolites. The mean terminal elimination half-life of norethisterone following a single oral dose administration is approximately 9,9 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 ethinylestradiol are co-administered, an increase in norethisterone serum levels can occur because of the binding of norethisterone to SHBG.

5.3 Preclinical safety information

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, which is not already included in other relevant sections. 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 at high doses at the time of the development of the external genitalia. Since epidemiological studies show that this effect is relevant in humans after high doses, it must 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 indication of teratogenic effects were obtained from the studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Keep in well closed containers and protected from light. Store at or below 30 °C.

6.5 Nature and contents of container

Brown glass bottles with tamperproof polyethylene closures in a carton, or aluminium/PVC blisters in a carton.
Pack sizes of 30 or 150 tablets.

Not all pack sizes ay be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO
1609

8. REGISTRATION NUMBER

G3124 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Old medicine

10. DATE OF REVISION OF THE TEXT

13 September 2022