1. NAME OF THE MEDICINAL PRODUCT

Norcolut® tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg norethisterone

Excipients with known effect: lactose monohydrate (92.50 mg per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
Almost white, flat, bevelled edged tablets, debossed with "+" on one side, "NORCOLUT" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dysfunctional bleeding, primary and secondary amenorrhoea, premenstrual syndrome, mastopathy, timing of menstruation, endometriosis.

4.2 Dosage and method of administration

4.2.1 Method of administration

Oral use

4.2.2 Dosage regimen

The tablets are to be swallowed whole with some liquid.

If you forget a dose, wait until it is time to take the next prescribed dose. Do not take the missed dose. If you are worried, contact your doctor or pharmacist.

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

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

4.2.2.1 Dysfunctional bleeding

The administration of 1 tablet Norcolut 3 times daily over 10 days leads to the arrest of uterine bleeding not associated with organic lesions within 1-3 days. In individual cases, bleeding diminishes during the first few days after the commencement of tablet-taking and does not stop until about 5 days later. For the treatment to be successful, Norcolut administration should be continued regularly even after arrest of bleeding (up to a total of 30 tablets).

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

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

Missing arrest of haemorrhage. Heavy break through bleeding
If the bleeding does not stop in spite of regular tablet taking, an organic cause must be considered. This applies also in cases where after initial arrest of haemorrhage, fairly heavy bleedings still occur during tablet-taking.

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

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

4.2.2.2 Primary and secondary amenorrhoea

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

In order to induce a menstruation-like bleeding, an estrogen is to be given before the administration of Norcolut.

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

Commencement of treatment
An equivalent of 20 mg estradiol valerate i.m. injection on the 1st day of treatment and equivalent of 10 mg estradiol valerate i.m. injection on the 14th day of treatment, followed by 1 tablet Norcolut 2-3 times daily from the 19th to the 26th day of treatment. Withdrawal bleeding starts about the 28th day.

Continuation of treatment (over at least 2-3 cycles)
An equivalent of 10 mg estradiol valerate i.m. injection on the 6th and 16th days of the artificial cycle, followed by 1 tablet Norcolut twice daily from the 19th to the 26th day of the cycle (1st day of bleeding = 1st day of the cycle).

An attempt can then be made to stop the estrogen treatment and to induce a cyclical bleeding by the administration of 1 tablet Norcolut twice daily from the 19th to the 26th day of the cycle. Exception: Patients of whom it can be safely assumed that endogenous estrogen production is insufficient (primary amenorrhoea in gonadal dysgenesia).

PLEASE NOTE:
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.

4.2.2.3 Premenstrual syndrome, mastopathy

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

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

4.2.2.4 Timing of menstruation

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

Dosage: 1 tablet Norcolut 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. If it does not, the doctor must be consulted.

4.2.2.5 Endometriosis

Treatment is commenced on the 5th day of the cycle with 1 tablet Norcolut 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 4-6 months. During treatment, ovulation and menstruation do not occur. After discontinuation of hormone treatment a withdrawal bleeding will occur.

4.3 Contraindication

Norcolut should not be used in the presence of any of the conditions listed below, which are derived also from information on progestogen-only product and combined oral contraceptives (COCs).

Should any of the conditions appear during the use of Norcolut, the product should be stopped 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 ‘Special warnings and precautions for use’)
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement
- Presence or history of severe hepatic diseases as long as liver function values have not returned to normal.
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these (see ‘Interaction with other medicaments and other forms of interaction’)
- Presence or history of liver tumours (benign or malignant)

- Known or suspected sex hormone-dependent malignancies (e.g. of the genital organs or the breasts).
- Hypersensitivity to the active substances or any of the excipients
- Dublin Johnson syndrome
- Rotor syndrome
- History during pregnancy of idiopathic jaundice, severe pruritus or herpes gestations

4.4 Special warnings and special precautions for use

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefits analysis should be done before Norcolut 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 thromboembolic diseases. Therefore, one should keep the possibility of an increased thromboembolic risk in mind, particularly where there is a history of thromboembolic disease or in the presence of severe diabetes with vascular changes or sickle-cell anaemia.

Generally recognized 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 immobilization, major surgery or major trauma.

The increased risk of thromboembolism in the puerperium must be considered (for information of pregnancy and lactation see section 'Pregnancy and lactation').

Treatment 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 Norcolut. In isolated cases, these tumours have led to life-threatening intra-abdominal hemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking Norcolut.

- 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 Norcolut.

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

Norethisterone also has estrogenic properties due to its partial conversion to estrogen ethinylestradiol ("Pharmacokinetic properties"). There were no corresponding estrogen- 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 gynecological examination should be

performed prior to the initiation or reinstitution of the use of Norcolut, guided by the contraindications (section 'Contraindications') and warnings (section 'Special warnings and precautions'), and these should be repeated during the use of Norcolut. 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), immobilization (for instance, following accidents), onset of jaundice, onset of anicteric hepatitis, generalized pruritus, significant rise in blood pressure, pregnancy.

4.4.1 Additional warnings based on the partial metabolisation of norethisterone to ethinylestradiol

After oral administration, norethisterone is partly metabolized to ethinylestradiol resulting in an equivalent dose of about 4-6 µg ethinylestradiol per 1 mg orally administered norethisterone / norethisterone acetate (see 'Pharmacokinetic properties').
Due to the partial conversion of norethisterone to ethinylestradiol, administration of Norcolut 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 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 1-2% 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.

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 discolored 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/m^2)
- 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, 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 (<50 µg ethinylestradiol).

- 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 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; hemolytic 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 medicaments and other forms of interaction

Note: The following interactions have been reported for combined oral contraceptives in the literature and may be relevant for Norcolut as well. The prescribing information of concomitant medications should be consulted to identify potential interactions.

Effects of other medicinal products on Norcolut

Interactions can occur with drugs 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 already be observed after a few days of treatment. Maximal enzyme induction is

generally seen within a few weeks. After the cessation of drug 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 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 medicinal product containing 35 µg ethinylestradiol.

Effects of Norcolut on other medicinal products

Progestogens may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) 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 weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

Pharmacodynamic interactions

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products 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 'Contraindications').

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

4.6.1 Pregnancy

The use of Norcolut during pregnancy is contraindicated.

4.6.2 Lactation

Norcolut should not be used during lactation.

4.7 Effects on ability to drive or use machines

Not known

4.8 Undesirable Effects

4.8.1 Summary of the safety profile

Undesirable effects are more common during the first months after start of intake of Norcolut, and subside with duration of treatment. In addition to the adverse effects listed in section "Special warnings and special precautions for use" the following undesirable effects have reported in users of Norcolut although a causal relationship could not always be confirmed.

4.8.2 Tabulated list of adverse reactions

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on reporting rates from postmarketing experience and literature.

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,* Hypomenorrhea*	Amenorrhea*			

General disorders and administration site conditions		Edema			

* in the indication Endometriosis

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

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.

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

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 estrogen-primed women with orally administered 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 Norcolut.

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

Due to the stabilizing effects of norethisterone on the endometrium, administration of Norcolut can be used to shift the timing of menstruation.

Like progesterone, norethisterone is thermogenic and alters the basal body temperature.

5.2 Pharmacokinetic properties

5.2.1 Absorption

Orally administered norethisterone is rapidly and completely absorbed over a wide dose range. Peak serum concentrations of about 16 mg/mL are reached within about 1.5 hours of administration of one tablet Norcolut. Due to a marked first-pass effect, the bioavailability of norethisterone after an oral dose is about

64%.

5.2.2 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 ± 1.3 L/kg. Following oral administration, the drug serum level time course follows a biphasic pattern. Both phases are characterized 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, irrespective of the route of administration. Based on a mean maximum drug level in maternal serum of about 16 mg/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.

5.2.3 Metabolism

Norethisterone is mainly metabolized 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 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 metabolized 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.

5.2.4 Elimination

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 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.

5.2.5 Steady-state conditions

During multiple-dose daily administration with norethisterone, an accumulation of the drug is unlikely because of the relatively short half-life of the drug. If, however, SHBG inducing agents such as ethinylestradiol are co-administered, an increase in norethisterone serum levels can occur because of the binding of norethisterone to SHBG.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch
Magnesium stearate
Silica colloidal anhydrous
Gelatine
Talc
Maize starch
Lactose monohydrate (92.50 mg).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Storage condition

Store below 30^0C. Protect from light and moisture.

6.5 Presentation

Name and Address of Manufacturer
Gedeon Richter Plc.
H-1103 Budapest
Gyömrői út 19-21.
Hungary

Date of revision of the text
May 2023

Package
20 tablets