PACKAGE INSERT

Brand or Product Name

NORCOLUT TABLET 5 MG

Name and Strength of Active Substance(s)

Each tablet contains 5 mg norethisterone.

Product Description

White or almost white, round flat, bevelled edged tablets, debossed with „+" on one side, "NORCOLUT" on the other side.

Pharmacodynamics/Pharmacokinetics

Pharmacodynamics
Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens.
ATC code: G03DC02

Norethisterone is a synthetic progestogen of the 19-nortestosterone group and has similar effects to those of natural progesterone, including suppression of gonadotropins, ovulation inhibition and endometrial transformation. Norethisterone is a first-generation progestin of low progestational and slight oestrogenic activity. It has weak androgenic properties.

Pharmacokinetics
Absorption
Norethisterone is well absorbed from the intestinal tract. Its absolute bioavailability ranged from 47% to 73%.

Distribution
Norethisterone is extensively binding to proteins: 61% to albumin and 36% to sex hormone binding globulin (SHBG).

Biotransformation
Norethisterone is metabolized in the liver via hydroxylation mainly by CYP3A4.
After the deacetylation of norethisterone acetate to norethisterone, norethisterone undergoes hepatic reduction and conjugation. 5-alpha-reductase plays an important role in the metabolism of norethisterone. Since norethisterone is partially metabolized via hydroxilation by CYP3A4, inhibitors and inducers of CYP3A4 can significantly alter circulating levels of norethisterone.
The most important metabolites of norethisterone are several isomers of 5-alpha-dihydro-norethisterone and tetrahydro-norethisterone, which are excreted mainly as glucuronide conjugates. Norethisterone and some of its metabolites are conjugated by the 17-beta-hydroxy group. Low serum ethinyloestradiol levels have been measured in postmenopausal women, following oral administration of relatively large doses of norethisterone acetate or norethisterone. On the basis of AUCs determined for ethinyloestradiol and norethisterone, it was shown that the mean conversion ratio of norethisterone to ethinyloestradiol was 0.7% and 1.0% at doses of 5 and 10 mg, respectively. This results in an equivalent dose of about 4-6 micrograms ethinyloestradiol per 1 mg of orally administered norethisterone or norethisterone acetate.

Elimination
The half-life of norethisterone is around 8 to 9 hours, its peak time is around 2 hours (varies by dose and use of concomitant oestrogen). The majority of norethisterone is excreted via urine (>50% as metabolites) and faeces (20% to 40% as metabolites).

Indications

- Heavy menstrual bleeding (menorrhagia/hypermenorrhoea)
- Cystic glandular hyperplasia of endometrium
- Inhibition of lactation

Recommended Dosage

Posology

For heavy menstrual bleeding (menorrhagia/hypermenorrhoea): 15 mg/day norethisterone from days 5th to 26th of the menstrual cycle is recommended.

For cystic glandular hyperplasia of endometrium: daily 10-15 mg norethisterone is recommended for 6-12 days from the 16th day of the cycle.

Inhibition of lactation: the dosing scheme of norethisterone for inhibition of lactation is described below at Table 1a and Table 1b:

Dosing scheme of Norcolut to prevent lactation

Dosing day	During weeks 16-28 in interrupted pregnancies	During weeks 28-36 in interrupted pregnancies
Day 1	15 mg (3 tablets)	15 mg (3 tablets)
Days 2-3	10 mg (2 tablets)	10 mg (2 tablets)
Days 4-7	5 mg (1 tablet)	10 mg (2 tablets)

Dosing scheme of Norcolut for ablactation:

Dosing day (day after delivery)	
Day 1-3	20 mg (4 tablets)
Days 4-7	15 mg (3 tablets)
Days 8-10	10 mg (2 tablet)

Special populations

Patients with renal impairment
No studies have been performed in patients with renal insufficiency.

Patients with hepatic impairment
No studies have been performed in patients with hepatic insufficiency.

Elderly
No studies have been performed in elderly patients (>65 years).

Paediatric population
Limited amount of data are available, therefore the use of Norcolut is not indicated in children.

Route of Administration

Oral use.
The tablets are to be swallowed whole with some liquid.

Contraindications

Norcolut should not be used in the presence of any of the conditions listed below. If any of these conditions appear during the use of Norcolut, the use of the preparation must be discontinued immediately:

Presence or risk of venous thromboembolism (VTE)
- Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g., deep venous thrombosis [DVT] or pulmonary embolism [PE]).
- Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
- Major surgery with prolonged immobilisation (see section "Warnings and Precautions").
- A high risk of venous thromboembolism due to the presence of multiple risk factors (see section "Warnings and Precautions").

Presence or risk of arterial thromboembolism (ATE)
- Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris).
- Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA).
- Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- History of migraine with focal neurological symptoms.
- A high risk of arterial thromboembolism due to multiple risk factors (see section "Warnings and Precautions") or to the presence of one serious risk factor such as:
  - diabetes mellitus with vascular symptoms
  - severe hypertension
  - severe dyslipoproteinaemia.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- 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-steroid influenced malignancies (e.g. of the genital organs or the breasts);
- Undiagnosed vaginal bleeding.
- Pregnancy and lactation.
- Idiopathic jaundice or severe pruritus during pregnancy.
- Hypersensitivity to the active substances or to any of the excipients.

Norcolut is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir. Norcolut is also contraindicated for concomitant use with the medicinal products containing glecaprevir/pibrentasvir (see sections "Warnings and Precautions" and section "Interactions with Other Medicaments").

Warnings and Precautions

Before administration thorough mammary and gynaecological examination, as well as oncological control are necessary.

Medical examination

Prior to the initiation of Norcolut a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications, and warning. The medical examination should include measuring blood pressure, examination of the breasts, abdomen and internal and external genital organs, a cervical smear and appropriate laboratory tests. The frequency and nature of these assessments should be based upon relevant guidelines which should be adapted to the individual woman.

Ethinyloestradiol is an active metabolite of norethisterone, therefore the general warnings associated with the use of ethinyloestradiol should also be considered. If any of the conditions or risk factors mentioned below is present, the therapy with Norcolut should be discontinued immediately.

Venous thromboembolism

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. Differences exist between CHCs in their risk of VTE depending on the type of progestogen they contain. Currently available data indicate that CHCs containing the progestogens levonorgestrel, norethisterone or norgestimate have the lowest risk of VTE.

Out of 10,000 women who are using a combined hormonal contraceptive that contains levonorgestrel, norethisterone, or norgestimate about 5-7 will develop a blood clot in a year.

Careful consideration should be given to the individual woman's current risk factors when prescribing a CHC, particularly those for VTE, and the difference in risk of VTE between products. CHCs are contraindicated if a woman has any serious risk factors that put her at high risk of blood clots.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. The treatment with steroid hormone may add to this risk.
A patient who develops symptoms suggestive of thromboembolic complications should stop treatment immediately. The need for treatment should be reassessed before continuing therapy.
Generally recognised risk factors for venous thromboembolism (VTE) include:

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m^2).	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma. Note: temporary immobilisation	In these situations it is advisable to discontinue use of the patch/pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Norcolut has not been discontinued in advance.

including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g., before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Other medical conditions associated with VTE.	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age.	Particularly above 35 years.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.
The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information on "Statement on usage during pregnancy and lactation").

Where a patient is already taking anticoagulants, the risk and benefits of progestogen therapy should be carefully considered.

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:
- unilateral swelling of the leg and/or foot 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 be associated with haemoptysis;
- sharp chest pain;
- 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).
Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.
If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Arterial thromboembolic events

Risk factors for ATE

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users

increases in women with risk factors (see table). Norcolut is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section "Contraindications"). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section "Contraindications").

Table: Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years.
Smoking	Women should be advised not to smoke if they wish to use any sex hormones or a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors.
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g., below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.
Other medical conditions associated with adverse vascular events.	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

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 trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (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;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

Liver tumours
In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnosis and, if necessary, the preparation should be withdrawn.

Acute or chronic disturbances of liver function may necessitate the discontinuation of Norcolut 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 Norcolut.

Cervical cancer
The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of sex hormones 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. sexual behaviour.

Breast cancer
Epidemiological studies reported that there is a slightly increased relative risk of having breast cancer diagnosed in women who are currently using products containing sex hormones. The excess risk gradually disappears during the course of the 10 years after cessation of the use of sex hormones. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent users of products containing sex hormones is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Hyperlipidaemias
Oestrogen may slightly increase trygliceride levels, therefore women with hypertriglyceridemia, or a family history thereof, may be at increased risk of pancreatitis.

Increase in blood pressure
Although small increases in blood pressure have been reported in many women taking products containing sex hormones clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a Norcolut then it is prudent for the physician to withdraw the norethisterone and treat the hypertension.
However sex hormone-induced hypertension is not common, its recognition is important because hypertensive women using Norcolut appear to be at increased risk of MI and stroke relative to nonusers.

Depression
Progestins may cause or exacerbate depressive symptoms in certain subpopulations of women, including those with a history of premenstrual syndrome or mood disorders. Therefore, it is suggested that clinicians should often monitor the patients with depression and the drug should be discontinued if the depression recurs to a serious degree.

Carbohydrate metabolism
Although oestrogen and progestogen may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using sex hormones. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment.

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

The use of exogenous hormone may be a contributing factors of chloasma especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should minimise exposure to the sun or ultraviolet radiation when taking Norcolut.

Oestrogens and progestogens may cause fluid retention. Special care should be taken when prescribing norethisterone in patients with conditions which might be aggravated by this factor: epilepsy, migraine, asthma, cardiac dysfunction, renal dysfunction.

There are inconsistent data in the scientific literature about the role of exogenous hormone in the development of inflammatory bowel disease (Chron's disease, ulcerative colitis). However, cessation of Norcolut use should be considered in those women who remain symptomatic despite conventional drug therapy.

If menstrual bleeding should fail to follow a course of Norcolut, or if the patient wishes to postpone menstruation in special circumstances, the possibility of pregnancy must be excluded before a further course is given.

The following conditions have been reported to occur or deteriorate with both pregnancy and exogenous hormone use, but the evidence of an association with the use of sex hormones is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinyloestradiol-containing medications (see sections "Contraindications" and "Interactions with Other Medicaments").
ALT elevations were also observed during concomitant use of combination glecaprevir/pibrentasvir and CHCs containing ethinyloestradiol in clinical trials (see sections "Contraindications" and "Interactions with Other Medicaments").

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

Interactions with Other Medicaments

Potential for other medicinal products to affect norethisterone

Antibacterials

Rifampicin, rifabutin and rifamycin derivates may enhance the metabolism of progestins and decrease the serum concentration of norethisterone by liver enzymes inductions.

Antiepileptics
Antiepileptic drugs increase the clearance of progestins by enzyme induction, so diminishing their effect. Oxcarbazepine, carbamazepine, eslicabazepin, clobazam, perampanel, primidone, topiramate, rufinamid, felbamate, lamotrigine, phenytoin and phosphenytoin reduce the serum concentrations of norethisterone.

Antivirals
Antiretroviral drugs such as protease inhibitors (e.g. lopinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) may decrease the serum concentration of progestins. A number of antivirals (ribavirin, darunavir, efavirenz, fosamprenavir, lopinavir, nelfinavir, saquinavir, telaprevir) are likely to accelerate the metabolism of progestogens, therefore they reduce the efficacy of norethisterone. In contrast to the above mentioned antiretroviral drugs, the following drugs may increase the serum concentration of progestins: atazanavir, cobicistat, boceprevir or tripranavir.

Antifungal
However, griseofulvin may reduce the efficacy of progestogens, voriconazole may increase the serum concentration of progestins.

Other
There are some antidiabetic, retionoid, antiemetic, antimalarial and anticancer drugs which may reduce the effect of progestins (e.g. lixisenatide, exenatide, metreleptin, acitrecin, fosaprepitan, aprepitant, artemether, bexarotene, brigatininb, ixazomib). Bile acid sequestrant, colesevelam, prucalopride, sugammadex, lumacaftor, mifepriston, ulipristal, mycophenolate and lesinurad may decrease the serum concentration of progestins also.

5-alpha-reductase inhibitors such as finasteride and dutasteride can inhibit the metabolism of norethisterone.

St John's Wort (*Hypericum perforatum*), bosentan, deferasirox, mitotane, sarilumab, siltuximab and tocilizumab may decrease the serum concentration of CYP3A4 substrates which may alter circulating levels of norethisterone.

Concomitant lamotrigine and progestins use may result in reduced plasma concentrations of lamotrigine, possibly resulting in reduced seizure control.

<u>Potential for norethisterone to affect other medicinal products</u>
Progestins may diminish the therapeutic effect of anticoagulants. More specifically, the potential prothrombotic effects of some progestins and progestin-oestrogen combinations may counteract anticoagulant effects of warfarin and phenindione.
Progestins may enhance the thrombogenic effect of C1 inhibitors, tranexamic acid, thalidomid and pomalidomide.

Norethisterone may diminish the therapeutic effect of antidiabetic agents.
Norethisterone may increase the serum concentration of voriconazole. Progestins may enhance the hepatotoxic effect of cyclosporine.

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations. Concomitant use with the medicinal products containing glecaprevir/pibrentasvir may also increase the risk of ALT elevations (see sections "Contraindications" and "Warnings and Precautions").

Laboratory tests
The use of sex steroids 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.

Statement on usage during pregnancy and lactation

Pregnancy
The administration of Norcolut during pregnancy is not indicated.

Since reproduction toxicity studies showed the risk of masculinisation in female foetuses when administered at high doses of norethisterone at the time of the development of the external genitalia, it must be stated that Norcolut may provoke signs of virilisation in female foetuses if administered during the hormone-sensitive stage of somatic sexual differentiation. Apart from this, no indications of teratogenic effects were obtained from the studies.

Breast-feeding
No case reports or epidemiological studies on norethisterone are available for use in breastfeeding. Norethisterone should be avoided in breastfeeding.

Adverse Effects/ Undesirable Effects

The following table gives a short summary on side effects related to norethisterone.

System Organ Class	**Adverse reactions**
Immune system disorders	Anaphylactic reaction, Hypersensitivity
Psychiatric disorders	Depression
Nervous system disorders	Dizziness, Headache, Migraine
Eye disorders	Visual disturbances
Vascular disorders	Cerebral embolism, Cerebral thrombosis, Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism
Gastrointestinal disorders	Abdominal pain, Nausea, Vomiting
Hepatobiliary disorders	Jaundice cholestatic
Skin and subcutaneous tissue disorders	Acne, Alopecia, Chloasma
Musculoskeletal and connective tissue disorders	Pain in extremity
Reproductive system and breast disorders	Amenorrhoea, Dysmenorrhoea, Menstrual disorder, Breakthrough bleeding, Breast enlargement, Breast tenderness, Breast soreness, Genital discharge, Breast pain, Ovarian cyst
General disorders and administration site conditions	Oedema
Investigations	Weight gain

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.

Overdose and Treatment

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives which contain norethisterone by young children. Overdose may cause nausea, and withdrawal bleeding may occur in females.
There are no antidotes and further treatment should be symptomatic.

Storage Conditions

Store below 30°C.

Dosage forms and packaging available

20 tablets are packed into folded carton box (10 tablets per blister).

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

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