Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Norethisterone 5 mg Tablets

norethisterone

PL 44041/0228

NOUMED LIFE SCIENCES LIMITED

LAY SUMMARY

Norethisterone 5 mg Tablets
norethisterone

This is a summary of the Public Assessment Report (PAR) for Norethisterone 5 mg Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Norethisterone 5 mg Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Norethisterone 5 mg Tablets and what are they used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Primolut N' (Norethisterone) 5 mg Tablets.

Norethisterone tablets can be used in several different circumstances to treat:

- irregular, painful or heavy periods
- endometriosis (where tissue from the lining of the womb is present in places where it is not normally found)
- premenstrual syndrome (also known as premenstrual tension, PMS or PMT).

This medicine can also be used to delay periods.

How do Norethisterone 5 mg Tablets work?
Norethisterone tablets contains Norethisterone, which belongs to a group of medicines called progestogens, which are female hormones.

How are Norethisterone 5 mg Tablets used?
The pharmaceutical form of this medicine is tablets and the route of administration is oral (by mouth). The tablets should be swallowed whole with a drink of water.

The number of tablets that are needed and the number of days per month to take them will depend on why the doctor has prescribed this medicine. A common dosage would be 2 to 3 tablets each day. For some conditions, this medicine has to be taken every day but this is not always the case.

For further information on how Norethisterone 5 mg Tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Norethisterone 5 mg Tablets have been shown in studies?
Because Norethisterone 5 mg Tablets is a generic medicine, studies in healthy adult female volunteers have been limited to tests to determine that it is bioequivalent to the reference

medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Norethisterone 5 mg Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Norethisterone 5 mg Tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why were Norethisterone 5 mg Tablets approved?
It was concluded that, Norethisterone 5 mg Tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Norethisterone 5 mg Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Norethisterone 5 mg Tablets. The RMP details the important risks of Norethisterone 5 mg Tablets, how these risks can be minimised, any uncertainties about Norethisterone 5 mg Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The safety concerns in the table on the following page have been recognised for Norethisterone 5 mg Tablets.

Summary of safety concerns	
Important identified risks	• Hypersensitivity to norethisterone, or any of the excipients. • Use during pregnancy and Lactation. • Use in patients with previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism). • Use in patients with active or recent arterial thromboembolic disease (e.g., angina, myocardial infarction). • Use in patients with presence or a history of prodromi of a thrombosis (e.g., transient ischaemic attack, angina pectoris). • Use in patients with a high risk of venous or arterial thrombosis • Use in patients with history of migraine with focal neurological symptoms. • Use in patients with Diabetes mellitus with vascular involvement. • Use in patients with presence or history of severe hepatic disease. • Use in patients with known, past or suspected sex hormone-dependent malignancies, including of the genital organs or breast cancer. • Use in patients with history during pregnancy of idiopathic jaundice or severe pruritus. • Use in patients with undiagnosed genital bleeding. • Use in patients with untreated endometrial hyperplasia
Important potential risks	• Increased blood pressure • New onset of migraine-type headaches • Sudden perceptual disorders (e.g., disturbances of vision or hearing) • Onset of jaundice or deterioration in liver function, anicteric hepatitis, general pruritus
	• Thrombophlebitis or thromboembolic symptoms. • Circulatory disorders • Benign and malignant liver tumours • Depression • Insulin resistance/decreased glucose tolerance
Missing information	• None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Norethisterone 5 mg Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Norethisterone 5 mg Tablets

A marketing authorisation for Norethisterone 5 mg Tablets was granted in the United Kingdom (UK) on 31 October 2024.

The full PAR for Norethisterone 5 mg Tablets follows this summary.

This summary was last updated in November 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Norethisterone 5 mg Tablets (PL 44041/0228) could be approved.

The product is approved for the following indications:

- metropathia haemorrhagica
- premenstrual syndrome
- postponement of menstruation
- endometriosis
- menorrhagia
- dysmenorrhoea.

Norethisterone has progestational actions similar to those of progesterone but is a more potent inhibitor of ovulation and has weak oestrogenic and androgenic properties. It is used to treat a number of disorders of the menstrual cycle.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Primolut N' (Norethisterone) 5 mg Tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Norethisterone 5 mg Tablets was granted in the United Kingdom (UK) on 31 October 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of 5 mg of norethisterone.

In addition to norethisterone, this product also contain the excipients cellulose microcrystalline, maize starch, ethyl cellulose and magnesium stearate.

The finished product is packaged Alu/PVC/PVdC Blister packs of 30, 72, 90 & 180 tablets. Not all pack sizes may be marketed.

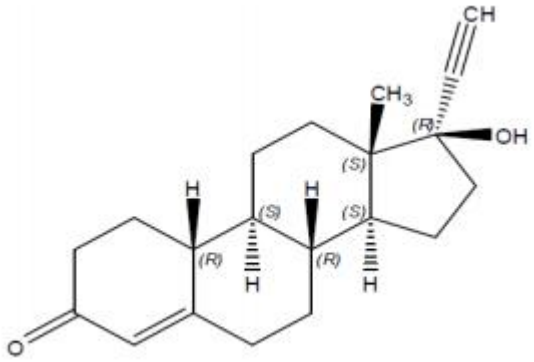
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: norethisterone

Chemical Name: 19-Norpregn-4-en-20-yne-3-one, 17-hydroxy-, (17α)
Or
17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one

Molecular Formula: $C_{20}H_{26}O_2$



Chemical Structure:

Molecular Weight: 298.42

Appearance: White or yellowish-white, crystalline powder

Solubility: Practically insoluble in water, soluble in tetrahydrofuran and in methylene chloride, sparingly soluble in acetone and in ethanol.

Norethisterone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months with no special storage conditions is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of norethisterone are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of norethisterone is well-known. With the exception of data from bioequivalence study C1B01557, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following:

Bioequivalence study C1B01557
This study was an open label, randomised, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study comparing the test product Norethisterone 5 mg Tablets versus the reference product Primolut N' (Norethisterone) 5 mg Tablets in healthy adult female subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single oral dose of either the test or reference product according to the randomisation schedule. Blood samples were taken pre-dose and up to 48 hours post dose in each period, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic Parameters (Units)	Ln- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)		ISCV (%)	Power (%)
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper		
C_{max} (ng/mL)	12.953	14.846	87.25	83.05	91.66	16.257	0.8963
AUC_t (µg/mL)*(hr)	134.225	143.919	93.26	89.02	97.71	15.332	0.9999

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with norethisterone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**