

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Noristerat® 200mg, solution for intramuscular injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml Noristerat contains 200mg norethisterone enantate in oily solution.

Excipient with known effect:

333.8 mg benzyl benzoate in 1 ml ampoule.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Noristerat is a depot contraceptive. It is intended for short-term use when a high level of efficacy independent of possible errors by the patient is required. It has been licensed for short-term use by women whose partners undergo vasectomy, until the vasectomy is effective, and women immunised against rubella, to prevent pregnancy during the period of activity of the virus.

Use after delivery or abortion: Noristerat can generally be used immediately after delivery or abortion (but see Section 4.6 '*Use during lactation*').

4.2 Posology and method of administration

200 mg Noristerat intramuscularly provides contraception for eight weeks. The first injection should be given within the first five days of a menstrual cycle (the first day of menstruation counting as day 1), unless it is given so

soon after delivery or abortion that no possibility of pregnancy exists. Provided the injection is carried out according to these instructions, no additional contraceptive cover is required. The injection may be repeated once, after eight weeks. Noristerat must always be injected deep into the gluteal muscles, care being taken that no liquid runs back from the injection site, which could result in loss of efficacy. The viscosity of the liquid at low temperatures is high, necessitating considerable pressure of injection. Therefore it is suggested that the ampoule be immersed in warm water before injection. A needle of at least medium bore should be used, and care taken to ensure that the needle is securely attached to the syringe. The injection must be administered extremely slowly (see Section 4.4 Special Warnings and Precautions for use).

4.3 Contraindications

- Known or suspected pregnancy.
- Current or severe hepatic disease as long as liver function values have not returned to normal.
- Previous or existing liver tumours.
- Severe diabetes with vascular changes.
- Pathologically increased blood pressure.
- Current thromboembolic disease.
- Disturbances of lipid metabolism.
- Suspected, existing or treated breast or endometrial cancer.
- Porphyria
- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Medical Examination

Assessment of women prior to starting Noristerat (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

Before starting treatment, pregnancy must be excluded.

Women should be advised that progestogen-only contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Gynaecological considerations

Noristerat should not be used in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital tract malignancy eliminated. Undiagnosed vaginal bleeding that is suspicious for underlying conditions should be investigated prior to first injection and endometrial pathology should be excluded if it occurs in women over 40 after prolonged amenorrhoea.

If there is a history of ectopic pregnancy or one fallopian tube is missing, the use of Noristerat should be decided on only after carefully weighing the benefits against the risks.

If obscure lower abdominal complaints occur together with an irregular cycle pattern (above all amenorrhoea followed by persistent irregular bleeding), an extrauterine pregnancy must be considered.

The patient should be informed before starting Noristerat that her menstrual pattern is likely to alter during the entire exposure period. Menstrual changes in the form of spotting, breakthrough bleeding and delayed menstruation are relatively frequent, and generally do not require treatment.

Amenorrhoea: if, when the second injection is due, bleeding has not occurred in the preceding eight weeks the second injection should not be given until pregnancy has been ruled out.

Partial metabolism of norethisterone to ethinylestradiol

Norethisterone is partly metabolised to ethinylestradiol (EE) after intramuscular administration in humans. This conversion results in a systemic EE exposure corresponding to an oral equivalent dose of about 4 µg EE per day, on average, over 8 weeks. Mean oral equivalent doses per day are about 10 µg EE during the first 2 weeks after Noristerat administration and decline to about 5 µg EE in the 3rd week and about 2 µg EE from the 5th week onwards. Therefore, systemic estrogen effects cannot be excluded (see section 5.2). Post-marketing experience with Noristerat indicates that the safety profile of Noristerat does not resemble that of combined hormonal contraceptives.

Circulatory disorders:

There is a general opinion, based on statistical evidence, that users of hormonal contraceptives experience, more often than non-users, venous thromboembolism, arterial thrombosis, including cerebral and myocardial infarction, and subarachnoid haemorrhage. Full recovery from such disorders does not always occur, and it should be realised that in a few cases they are fatal.

The relative risk of arterial thrombosis (e.g. stroke and myocardial infarction) appears to increase further when heavy smoking, increasing age and the use of hormonal contraceptives coincide.

Although there have been so far no observations of thromboembolic disease during the use of Noristerat, as a precaution it is recommended that this preparation should not be used where there is a history of thromboembolic processes.

No further injection should be given if symptoms of an arterial or venous thrombotic event occur during treatment, e.g.

- new onset or exacerbation of migraine-type headaches,
- sudden disturbances of vision or hearing perceptual disorders occur,
- significant rise in blood pressure,
- first signs of thrombosis or blood clots.

Liver Function

Porphyria and existing impairment of liver function might theoretically be exacerbated by Noristerat.

In rare cases benign, and in even rarer cases malignant, liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage, have been observed after the use of hormonal substances such as the one contained in Noristerat. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be considered in the differential diagnosis.

Women with a history of disturbed liver function or any disease that is prone to worsen during pregnancy such as idiopathic jaundice or severe pruritus of pregnancy should be carefully observed during medication.

Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of Noristerat.

Other conditions

A reduction of glucose tolerance has been observed in some women using progestogens. Consequently, diabetics and women with a tendency to diabetes should be carefully supervised during the use of Noristerat. In the case of diabetes, it may be necessary to reassess the required doses of antidiabetics or insulin.

In rare cases coughing, dyspnoea and circulatory irregularities may occur during or immediately after the injection. Experience has shown that these reactions can be avoided by injecting Noristerat very slowly.

Women with a history of severe depressive states should be carefully observed during medication. No further injection should be given, if during treatment, recurrence of earlier depression is experienced.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Effect on blood chemistry: No influence of Noristerat on basal plasma cortisol, the ACTH test or the metyrapone test has been observed. In the acute dexamethasone suppression test, however, a higher plasma cortisol value than expected was found in

4 out of 10 women, although there were no clinical indications of disturbed adrenocortical function. A shortening of the recalcification time and of the thromboplastin time (Quick's test) were observed in studies of the blood coagulation system.

Information about excipients

This medicine contains 333.8 mg benzyl benzoate in each 1 ml ampoule.

Benzyl benzoate may increase jaundice in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interaction

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

There are no data on progestogen-only injectables drug interactions.

Effects of other medicinal products on Noristerat

Substances increasing the clearance of sex hormones (enzyme inducers)

Direct clinical evidence for reduced effectiveness of Noristerat has not been obtained. However, theoretical interactions based on findings with combined oral contraceptives include the following, which have been shown to have clinically important interactions:

Anticonvulsants: phenytoin, barbiturates, primidone, carbamazepine, phenylbutazone, oxcarbazepine, topiramate, felbamate.

Antifungal agents: griseofulvin.

Certain antibiotics: rifampicin and ampicillin (possibly due to changes in the intestinal flora).

Herbal remedies: products containing St John's wort (*Hypericum perforatum*).

Antiviral agents: HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can have variable effects on the plasma concentrations of sex hormones.

Substances decreasing the clearance of sex hormones (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole) and macrolides (e.g. erythromycin) can increase plasma concentrations of the progestin.

Effects of Noristerat on other medicinal products

Hormonal contraceptives may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may be affected (e.g. increased ciclosporin plasma concentrations).

The requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.

Other forms of interaction

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. Since norethisterone is partly metabolised to ethinylestradiol after intramuscular Noristerat administration in humans (see section 5.2) such an interaction cannot be excluded.

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests.

4.6 Pregnancy and lactation

Pregnancy

Noristerat is contraindicated in pregnancy.

Like all nortestosterone derivatives used for contraception, Noristerat has slight androgenic activity, and a virilising effect on the external genitalia of a female foetus exposed to Noristerat after the first month of pregnancy cannot be totally ruled out on theoretical grounds. However, no such virilisation has been observed after the few pregnancies that have been reported during the use of Noristerat.

Lactation

There appear to be no adverse effects on infant growth or development when using Noristerat after six weeks postpartum. Noristerat does not appear to affect the quantity or quality of breast milk, however, minute amounts of the active substance are excreted with the milk and although considered harmless to a healthy neonate, might theoretically, like other steroids impair the degradation of bilirubin especially during the first week of life. If the mother has received Noristerat, breast-feeding should therefore be withheld from neonates with severe or persistent jaundice requiring medical treatment.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Undesirable effects that have been reported in users of Noristerat (based on post-marketing data) are:

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 and < 1/10	Uncommon ≥ 1/1.000 and < 1/100
Immune system disorders		Hypersensitivity reaction	
Metabolism and nutrition disorders		Weight increase	
Psychiatric			Depressed mood

disorders			
Nervous system disorders		Dizziness Headache	
Gastrointestinal disorders		Nausea	
Skin and subcutaneous tissue disorders		Skin disorder	
Reproductive system and breast disorders	Uterine / Vaginal bleeding including Spotting Amenorrhoea (short lasting)		breast discomfort
General disorders and administration site conditions		Injection site reaction Local skin reaction	Bloating

Administration-related events:

Experience has shown that the short-lasting reactions (urge to cough, paroxysmal cough, respiratory distress, dyspnoea and circulatory irregularities) may occur in isolated cases during or immediately after the injection of oily solutions if the solution is injected too rapidly (see Section 4.4).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Presentation of a single use injectable and administration by a physician minimize the risk of overdose. There have been no reports of serious deleterious effects from overdose. There are no antidotes and further treatment should be symptomatic

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens ATC code: None assigned

Mechanism of action

Noristerat is a depot contraceptive. The mode of action, following injection, is initially inhibition of ovulation.

Towards the end of the injection interval, the action is mainly local on the cervical mucus and endometrium. These latter effects prevent ascension of sperm into the uterine cavity and impede nidation.

5.2 Pharmacokinetic properties

Absorption

Norethisterone enantate was completely absorbed after intramuscular injection. The ester was quickly and eventually completely hydrolyzed to its pharmacologically active compound norethisterone once it was released from the depot.

Distribution

Maximum levels of norethisterone were measured about 3-20 days after i.m. administration. They amounted on average to 13.4 ± 5.4 ng/ml and 12.2 ± 2.7 ng/ml about 7 days (median) after i.m. administration of 200 mg norethisterone enantate in 2 ml and 1 ml oily solution, respectively.

Plasma levels of norethisterone declined in two disposition phases with half-lives of 4-5 days and 15-20 days, respectively, which were due to a biphasical release of norethisterone enantate from the depot.

Biotransformation

Norethisterone enantate is metabolised completely. Norethisterone enantate is split mainly in the liver by enzymatic hydrolysis into norethisterone and heptanoic acid.

While the fatty acid is metabolised by means of (β -oxidation, norethisterone is transformed mainly through the reduction of the C₄-C₅ double bond and the C₃ keto group. The majority of metabolites found in urine were present as conjugates, mainly as sulfates, which are expected to be inactive.

Norethisterone is partly metabolised to ethinylestradiol (EE) after intramuscular administration in humans. This conversion results in a systemic EE exposure corresponding to an oral equivalent dose of about 4 μ g EE per day, on average, over 8 weeks. Mean oral equivalent doses per day are about 10 μ g EE during the first 2 weeks after Noristerat administration and decline to about 5 μ g EE in the 3rd week and about 2 μ g EE from the 5th week onwards. Therefore systemic estrogen effects cannot be excluded. The C_{max} of EE after i.m. administration of 200 mg NETE was significantly lower than after oral administration of 0.03 mg EE/0.15 mg LNG once daily for 21 days (approximately 68% lower). Post-marketing experience with Noristerat indicates that the safety profile of Noristerat does not resemble that of combined hormonal contraceptives.

Elimination

Up to 85% of the norethisterone enantate dose were excreted within 30 days in urine (40%) and faeces (60%). No unchanged norethisterone enantate was recovered in urine or faeces. In urine and faeces, similar excretion half-lives of 6 - 9 days were estimated for radioactive labelled substances during the observation period of 30 days and - in a further study - an excretion half-life of 20 - 30 days was measured in urine between day 30 and 80 after i.m. administration of 200 mg ³H-norethisterone enantate. Based on animal studies, retention of the drug in the body is

not to be expected.

In plasma of women, 96% of norethisterone are bound to proteins. The respective percentages bound to SHBG and albumin are approximately 35% and 61% as long as SHBG levels are within the normal range.

Due to the half-life of the terminal disposition phase from plasma (about 2.5 weeks) and the initial dose regimen (one injection every 2 months), a slight accumulation of the drug will be expected after multiple administrations. A steady state will already be reached after the second administration.

Transfer of norethisterone into mother's milk was negligible. During the first week after i.m. injection of 200 mg norethisterone enantate, a daily intake of norethisterone with mother's milk in the range of 0.5 µg to 2.4 µg was calculated from norethisterone concentrates in the milk, assuming that the infant ingests 600 ml milk daily.

Linearity/non-linearity

Although there is no direct investigation on bioavailability of norethisterone after i.m. administration of norethisterone enantate reported, complete availability can be estimated by comparison of norethisterone AUC values determined in different studies after i.v. injection of norethisterone and after i.m. injection of norethisterone enantate.

5.3 Preclinical safety data

Non-clinical data reveal no special risk for humans based on studies of repeated dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction which is not already included in other relevant sections.

Besides the studies with the active ingredient norethisterone enantate, data recorded for norethisterone and norethisterone acetate were also taken into consideration for the toxicological evaluation of the risk from use of Noristerat.

In animal studies on systemic tolerance with repeated administration (including studies for evaluation of a tumorigenic activity), no systemic intolerance reactions were observed which would raise objections to the use of the preparation in dosages required for contraception.

On principle, however, it should be kept in mind that sex steroids might stimulate the growth of hormone-dependent tissues and tumours.

In reproduction toxicological studies no indication of a teratogenic potential was noted. This is in accordance with reports on clinical experience after accidental administration of Noristerat during pregnancy or on the rare cases of pregnancies occurring during use of Noristerat, where no indication of a teratogenic potential was noted.

Local tolerance was assessed in the course of systemic tolerance studies and indicated only a mild irritant potential of the drug substance. The good local tolerance has been confirmed by long-term clinical experience.

Experimental investigations into possible sensitising effects of norethisterone enantate have not been carried out.

In vitro studies for evaluation of genotoxicity did not indicate that norethisterone or its esters possess a mutagenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Castor oil for injection
Benzyl benzoate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Carton containing one 1ml glass ampoule.

6.6 Special precautions for disposal

Keep out of the reach of children.

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading

RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0548

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

23/02/2009

10 DATE OF REVISION OF THE TEXT

17/10/2019