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NAME OF THE MEDICINAL PRODUCT

Noristerat, 200 mg, solution for intramuscular injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

PHARMACEUTICAL FORM

Oily solution for intramuscular injection

CLINICAL PARTICULARS

Indication(s)

Hormonal contraception

Dosage and method of administration

How to use Noristerat

Noristerat, when used correctly, has a failure rate of approximately 1% per year. The failure rate may increase when intervals between injections are prolonged.

Noristerat must be administered always as a deep intramuscular injection (preferably intragluteal, alternatively into the upper arm). The injection must be administered extremely slowly .It is advisable to place a plaster over the injection site after the injection to prevent any reflux of the Noristerat solution.

How to start Noristerat

No preceding hormonal contraceptive use

Noristerat should be administered within the first 5 days of the woman's natural cycle, i.e. the first 5 days of the menstrual bleeding.

Changing from a combined oral contraceptive (COC)

Preferably, the woman should start with Noristerat immediately on the day after the last active tablet of her previous COC. When starting later she should be advised to additionally use a barrier method for the first 7 days after injection.

Changing from a progestogen only method (minipill, injection, implant) or from a progestogen-releasing intrauterine device (IUS)

The woman may switch any day from the minipill without break (from an implant or an IUS on the day of its removal, from another injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days after injection.

Following abortion or delivery

Noristerat may be used immediately after delivery or abortion as long as there are no medical objections.

For breastfeeding woman .

Management of next injections

The next three injections are to be given in intervals of 8 weeks, after which a further injection is required every 12 weeks (84 days). If the injection interval is extended beyond, no adequate contraceptive protection will be available from the 13th week onwards and the woman should be advised accordingly to use additional contraceptive measures.

Should technical reasons make it impossible to maintain the 84-day injection interval, a 2-month regimen can alternatively be adopted, as was done in an extensive WHO study .

In any case, if no withdrawal bleeding has occurred within the preceding 10 weeks, pregnancy must be ruled out by means of a suitable test.

Contraindications

Noristerat should not be used in the presence of any of the conditions listed below. Should any of the conditions appear during the use of Noristerat, no further injections should be given.

- Known or suspected pregnancy
- Active venous thromboembolic disorders
- Arterial and cardiovascular disease present or in history (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease)
- Pathologically increased blood pressure
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumors (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breast)
- Diabetes mellitus with vascular involvement

- Disturbances of lipometabolism
- Hypersensitivity to the active substance or to any of the excipients
- Undiagnosed vaginal bleeding

Special warnings and precautions for use

No epidemiological studies have been identified for Progestogen Only Injectable contraceptives (POIs) investigating risk factors to be included in this section. The general experience with progestogen-only pills regarding warnings and special precautions for use should be considered as a basis for POIs.

Warnings

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before Noristerat is started or continued.

- Circulatory Disorders

From epidemiological studies there is little evidence for an association between progestogen-only pills and an increased risk of myocardial infarction and cerebral thromboembolism. The risk of cardiovascular and cerebral events is rather related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only injectables.

Some recent studies indicated that there may be a slightly, but not statistically significant increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only pills. 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 and prolonged immobilization, major surgery or major trauma. In case of long-term immobilization it is advisable to discontinue the use of Noristerat (in the case of elective surgery, 12 weeks in advance) and not to resume until two weeks after complete remobilization. If possible, the timely discontinuation of Noristerat should be taken care of especially in women with e.g. known risk factors for thrombosis, in abdominal surgery, surgery of the lower limbs).

The increased risk of thromboembolism in the puerperium must be considered. For information on “Pregnancy and lactation” see section 4.6.

No further injection should be given in case of symptoms of an arterial or venous thrombotic event or suspicion thereof, if migrainous headaches occurs for the first time, if recurrent, unusually severe headaches or headaches with a new pattern develop, if sudden perceptual disorders (e.g. disturbances of vision or hearing) occur.

- Tumors

In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of hormonal contraceptives. In isolated cases, these tumors have led to life-threatening intraabdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women using Noristerat.

- Other conditions

Progestogen-only contraceptives generally do not appear to affect blood pressure in normotensive women. Small increases in blood pressure have been reported in women taking combined oral contraceptives and in one study using injectable contraceptives, however, clinically relevant increases are rare. If a sustained clinically significant hypertension develops, then it is prudent for the physician to stop using Noristerat and treat the hypertension. Where considered appropriate, the use of Noristerat 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 oral contraceptive use and may be considered for users of progestogen-only contraceptives, but the evidence of an association is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea.

Recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroid necessitates the discontinuation of Noristerat.

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 while using Noristerat.

If there is a history of extrauterine pregnancy or one 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 amenorrhea followed by persistent bleeding), an extrauterine pregnancy must be considered.

No further injection should be given, if during treatment, recurrence of earlier depression is experienced.

Although Noristerat may have a slight effect on peripheral insulin resistance and glucose tolerance there is generally no need to alter the therapeutic regimen in diabetics using progestogen-only contraceptives. However, diabetic women, also those with a history of gestational diabetes mellitus, should be carefully observed while using Noristerat.

- Partial metabolization of norethisterone to ethinylestradiol[i]

Norethisterone is partly metabolized to ethinylestradiol (EE) after intramuscular Noristerat 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 and does not exceed a mean maximum oral equivalent dose of 20 µg EE per day. Based on these data systemic estrogen effects cannot be excluded. Post-marketing experience with Noristerat indicates however that the safety profile of Noristerat does not resemble that of combined hormonal contraceptives.

Medical examination/ consultation

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 Noristerat, guided by the contraindications and warnings ,and these should be repeated at least annually during the use of Noristerat.

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.

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

Reduced efficacy

The efficacy of Noristerat may be reduced in the event of e.g. a prolonged injection interval or concomitant medication.

Reduced cycle control

Menstrual bleeding

Individually different cycle disturbances may occur during the treatment. If, however, the women are informed about this before the start of the treatment, these disturbances are rarely a reason for the withdrawal of Noristerat.

In general, the cycle under Noristerat does not change significantly in about 50 - 70 % of the women (bleeding intervals between 26 and 35 days, duration of bleeding 1 - 7 days). A tendency for the cycle to stabilize is observed with increasing duration of use.

- Amenorrhea

Amenorrhea occurred in 8 - 25 % of the women during clinical investigations. It was generally of short duration and disappeared again in the further course of treatment. The rate of amenorrhea did not increase with prolonged use.

If the use of Noristerat has been discontinued because of amenorrhea, further diagnostic measures are necessary to clarify the causes. If pregnancy can be ruled out and then amenorrhea continues, special treatment is required particularly in younger women.

- Procedure in the event of intermenstrual bleeding

Intermenstrual bleeding can occur either as spotting or with menstrual intensity. These disturbances need not concern the patient and do not impair the contraceptive reliability. Treatment is usually unnecessary.

If bleeding irregularities persist or occur after previous regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

Return of fertility

In clinical studies, ovulatory pattern are restored in most women within 12 weeks after discontinuation of Noristerat.

The normal ability to conceive usually returns about 4 - 5 months after the last injection.

If a physiological cycle pattern fails to develop within this period of time, appropriate treatment is indicated in women who want children.

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. Therefore, the following interactions are based on findings with combined oral contraceptives:

Effects of other medicinal products on Noristerat

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 contraceptive failure.

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.

Women on treatment with any of these drugs should temporarily use a barrier method in addition to Noristerat or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

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

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the 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. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice 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. cyclosporine).

Other forms of interaction

Laboratory tests

The use of contraceptive 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.

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Pregnancy and lactation

Pregnancy

The administration of Noristerat during pregnancy is contraindicated. If pregnancy occurs during treatment, further injections must not be given.

In earlier years, when estrane derivatives were being used at very high dosage for the maintenance of pregnancy, individual cases of virilization of the external sex characteristics of female neonates were also described following administration of preparations containing norethisterone, this being associated with the androgenic residual effect of these substances. Since it cannot be stated unequivocally that such a situation will not occur under Noristerat, injection during pregnancy - and particularly in the sensitive phase after the first month of pregnancy - is contraindicated. It must be added, however, that no such effect has been observed in the few pregnancies which have so far occurred during the wearing-off of the Noristerat effect.

Lactation

Hormonal contraceptives are not recommended as the contraceptive method of first choice during lactation, but progestogen-only methods are considered to comprise the next choice category after non-hormonal methods. There appear to be no adverse effects on infant growth or development when using any progestogen-only method after six weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk, however, minute amounts of the active substance are excreted with the milk.

Effects on ability to drive or use machines

No observed effects.

Undesirable effects

The most serious undesirable effects associated with the use of hormonal contraceptives are listed in section "Special warnings and precautions for use". Other undesirable effects that have been reported in users of Noristerat (postmarketing data) but for which the association to this preparation has neither been confirmed nor refuted 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 disorders			Depressed mood
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)		
General disorders and administration site conditions		Injection site reaction	

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

Respiratory, thoracic and mediastinal disorders

Experience has shown that the short-lasting reactions (Urge to cough, Paroxysmal cough, Respiratory distress) which occur in isolated cases during or immediately after the injection of oily solutions can be avoided by injecting the solution extremely slowly.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

The steroid hormone component of Noristerat, norethisterone enantate, exerts its contraceptive effect in several ways.

The most important ones are suppression of ovulation and changes in the cervical mucus which becomes more viscous and thick, posing an obstacle to sperm penetrability.

Throughout the cycle, also morphological changes in the endometrium can be considered as having the effect of rendering nidation of a fertilized egg difficult.

In clinical studies, Noristerat was generally injected at 12-week intervals. Contraceptive reliability was lower than for oral progestogen-estrogen preparations. Most of the pregnancies observed occurred within the first two injection intervals. The contraceptive reliability was distinctly better when the duration of use was longer. In addition, injecting Noristerat at intervals of 8 weeks at the start of treatment was found to improve its contraceptive effect.

Clinical studies into the effect on blood lipid fractions showed no significant alterations in serum triglycerides, total cholesterol, low density, and very low density lipoproteins, however, a reduction in mean serum high density lipoprotein level was found. Nevertheless, the ratio of total cholesterol to high density lipoprotein cholesterol was unchanged between controls and Noristerat user groups.

Pharmacokinetic properties

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.

Maximum levels of norethisterone were measured about 3 - 10 days after i.m. administration. They amounted on average to 13.4 $\pm$ 5.4 ng/ml and 12.2 $\pm$ 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 biphasic release of norethisterone enantate from the depot.

Norethisterone enantate is metabolized completely. Norethisterone enantate is split mainly in the liver by enzymatic hydrolysis into norethisterone and heptanoic acid. While the fatty acid is metabolized by means of ß-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 metabolized to ethinylestradiol (EE) after intramuscular Noristerat 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 and does not exceed a mean maximum oral equivalent dose of 20 µg EE per day. 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. Based on these data systemic estrogen effects cannot be excluded. However, post-marketing experience with Noristerat indicates that the safety profile of Noristerat does not resemble that of combined hormonal contraceptives.

Up to 85 % of the norethisterone enantate dose was excreted within 30 days in urine (40 %) and feces (60 %). No unchanged norethisterone enantate was recovered in urine or feces. In urine and feces, similar excretion half-lives of 6 - 9 days were estimated for radioactive labeled substances during the observation period of 30 days**Error! Bookmark not defined.** and - in a further study - an excretion half-life of 20 - 30 days was measured in urine between days 30 and 80 after i.m. administration of 200 mg -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 is 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 concentrations in the milk, assuming that the infant ingests 600 ml milk daily.

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[ii] and after i.m. injection of norethisterone enantate.

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. However, it should be kept in mind that sexual steroids might stimulate the growth of hormone-dependent tissues and tumors.

Besides the studies with the active ingredient norethisterone enantate, also the data which were recorded for the actual pharmacologically active metabolite of norethisterone enantate, norethisterone, or for another cleavable ester, norethisterone acetate were also taken into consideration for the toxicological evaluation of the risk from use of Noristerat.

In animal experimental 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 tumors.

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 either.

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

Experimental investigations into possible sensitizing 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Castor oil for injection
Benzyl benzoate

Incompatibilities

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

Nature and contents of container

Brown or colorless ampule of 1 ml, glass type I

Manufacturer

Site: Bayer Pharma AG, Berlin

Bayer Pharma AG

Müllerstraße 178

13353 Berlin

Germany

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Date of last revision of text

05/04/2016 CCDS version 7

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1. REFERENCES

[i] Höchel J, Gröttrup-Wolfers E, Justification Document No. 010 a+b – NET conversion to EE, dated 05 Apr 2016, LM 06 to CCDS 07

[ii] Back DJ et al. Kinetics of norethindrone in women. Clin Pharmacol Ther 1978;24:448-453