SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

NUR-ISTERATE 200 mg/ml oily solution for intramuscular injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains norethisterone enantate (17α-ethinyl-17β-heptanoyloxy-4-estrene-3-one) 200 mg.

Excipient with known effect:
333,8 mg benzyl benzoate in 1 ml ampoule.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oily solution for intramuscular injection

Clear, yellowish, oily solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hormonal contraception

4.2. Posology and method of administration

Posology

How to start NUR-ISTERATE

No preceding hormonal contraceptive use

NUR-ISTERATE 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

The woman should start with NUR-ISTERATE immediately on the day after the last active tablet of her previous combined oral contraceptive. 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

The woman may switch any day from the minipill without break (from an implant or an intrauterine system 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

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

For breastfeeding women see section 4.6.

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 this, 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.

Method of administration

NUR-ISTERATE must always be administered as a deep intramuscular injection (preferably intragluteal, alternatively into the upper arm deltoid muscle). The injection must be administered extremely slowly (see section 4.8). It is advisable to place a plaster over the injection site after the injection to prevent any reflux of the NUR-ISTERATE solution.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known or suspected pregnancy.
- Venous thromboembolic disorders or history thereof.
- Arterial and cardiovascular disease present or in history (e.g. myocardial infarction, cerebrovascular accident, ischaemic heart disease).
- Uncontrolled hypertension.
- Acute hepatic disease or history of severe hepatic disease as long as liver function values have not returned to normal.
- Primary biliary cirrhosis, Dubin-Johnson syndrome, Rotor syndrome.
- Presence or history of liver tumours (benign or malignant).
- History of idiopathic jaundice of pregnancy or severe pruritus of pregnancy.
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breast).
- Diabetes mellitus with vascular involvement.
- Disturbances of lipometabolism.
- Undiagnosed vaginal bleeding.
- Porphyria

4.4. Special warnings and precautions for use

Circulatory disorders

According to the present state of knowledge, an association between the use of hormonal contraceptives and an increased risk of venous and arterial thromboembolic diseases cannot be ruled out. The relative risk of arterial thromboses (e.g. stroke, myocardial infarction) appears to increase further when heavy smoking, increasing age and the use of hormonal contraceptives coincide. In women with hypertension the risk of

stroke may be slightly enhanced by NUR-ISTERATE.

There may be an increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of NUR-ISTERATE.
In case of prolonged immobilisation it is advisable to discontinue the use of NUR-ISTERATE (in the case of elective surgery, 12 weeks in advance) and not to resume until two weeks after complete remobilisation.

No further injection should be given

- if first signs of thrombophlebitis or thromboembolic disease (e.g. unusual pain in the legs or swelling of the legs, stabbing pains on breathing, or coughing for no apparent reason) are noted, or if a feeling of pain and tightness in the chest are experienced,
- in case of symptoms of an arterial or venous thrombotic event or suspicion thereof,
- if migrainous headaches occur 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.

Tumours

Cases of benign liver tumours, and malignant liver tumours have been reported in users of hormonal contraceptives. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women using NUR-ISTERATE.

Other conditions

Progestogen-only contraceptives such as NUR-ISTERATE generally do not appear to affect blood pressure in normotensive women. Small increases in blood pressure have been reported 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 NUR-ISTERATE and treat the hypertension. Where considered appropriate, the use of NUR-ISTERATE may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate, but the evidence of an association is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea.

Recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of NUR-ISTERATE.

Chloasma may occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should not use NUR-ISTERATE.

If there is a history of extrauterine pregnancy or one tube is missing, the use of NUR-ISTERATE 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 bleeding), an extrauterine pregnancy must be considered.

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

Although NUR-ISTERATE 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 NUR-ISTERATE.

Partial metabolism of norethisterone to ethinylestradiol

Norethisterone is partly metabolised to ethinylestradiol after intramuscular NUR-ISTERATE administration in humans. This conversion results in a systemic ethinylestradiol exposure corresponding to an oral equivalent dose of about 4 µg ethinylestradiol per day on average over 8 weeks. Mean oral equivalent doses per day are about 10 µg ethinylestradiol during the first 2 weeks after NUR-ISTERATE administration and decline to about 5 µg ethinylestradiol in the 3rd week and about 2 µg ethinylestradiol from the 5th week onwards. Mean maximum oral equivalent dose of 20 µg ethinylestradiol per day were not exceeded (see section 5.2). Based on these data systemic estrogen effects cannot be excluded. Post-marketing experience with NUR-ISTERATE indicates however that the safety profile of NUR-ISTERATE does not resemble that of combined hormonal contraceptives.

Medical examination/consultation

A complete medical history should be taken and a physical and gynaecological examination should be performed prior to the initiation or reinstitution of the use of NUR-ISTERATE, guided by the contraindications and warnings (see sections 4.3 and 4.4) and these should be repeated at least annually during the use of NUR-ISTERATE.
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 infections.

Reduced efficacy

The efficacy of NUR-ISTERATE will be reduced in the event of e.g. a prolonged injection interval (see section 4.2) or concomitant medication (see section 4.5).

Reduced cycle control

Menstrual bleeding

Individually different cycle disturbances commonly occurs 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 NUR-ISTERATE.

In general, the cycle under NUR-ISTERATE does not change significantly in about 50 to 70 % of the women (bleeding intervals between 26 and 35 days, duration of bleeding 1 to 7 days). However, only about 15 % will have consistently normal cycles.

Amenorrhoea

Amenorrhoea occurred in 8 to 25 % of the women during clinical investigations. It was generally of short duration and disappeared again in the further course of treatment. However, 0,5 % of women had persistent amenorrhoea for at least one year.

If the use of NUR-ISTERATE has been discontinued because of amenorrhoea, further diagnostic measures are necessary to exclude pregnancy or other causes. If pregnancy can be ruled out and then amenorrhoea 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.

Return to fertility

In clinical studies, ovulatory patterns are restored in most women within 12 weeks after discontinuation of NUR-ISTERATE.

The normal ability to conceive usually returns about 4 to 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.

4.5. Interaction with other medicines 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 injectable drug interactions. Therefore, the following interactions are based on findings with combined oral contraceptives:

Effects of other medicines on NUR-ISTERATE

Interactions can occur with medicines 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 treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of medicine therapy enzyme induction may be sustained for about 4 weeks.

Women on treatment with any of these medicines should temporarily use a barrier method in addition to NUR-ISTERATE or choose another method of contraception. The barrier method should be used during the time of concomitant medicine 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, rifabutin 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 NUR-ISTERATE on other medicines

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

Other forms of interactions

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.

4.6. Pregnancy and lactation

Pregnancy

The administration of NUR-ISTERATE during pregnancy is contraindicated (see section 4.3). If pregnancy occurs during treatment, further injections must not be given.

Virilisation of the external sex characteristics of female neonates were described following administration of preparations containing norethisterone, such as NUR-ISTERATE, this being associated with the androgenic residual effect of these substances. Since it cannot be stated unequivocally that such a situation will not occur with NUR-ISTERATE, injection during pregnancy – and particularly in the sensitive phase after the first month of pregnancy – is contraindicated.

Lactation

NUR-ISTERATE has no inhibiting influence on lactation. However, small quantities of NUR-ISTERATE may be eliminated with the milk. It is therefore possible that the degradation of bilirubin in neonates will be impaired, particularly during the first week of life. If the newborn is suffering from severe or persistent jaundice which requires medical treatment, breastfeeding must be interrupted for the time of treatment.
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.
Transfer of norethisterone into mother's milk is negligible. During the first week after IM injection 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.

4.7. Effects on ability to drive or use machines

NUR-ISTERATE may cause adverse reactions such as dizziness that may affect the ability to drive and use machinery. Patients should be advised not to drive and use machines if they feel dizzy.

4.8. Undesirable effects

Relatively frequent side effects are cycle disturbances in the form of spotting, excessive menstrual bleeding, breakthrough bleeding and amenorrhoea of short duration. These disturbances do not impair contraceptive reliability. Treatment should only be considered for persistent bleeding. Cycle disturbances are rarely reasons for withdrawal of NUR-ISTERATE.

System organ class	Very common (≥ 1/10)	Common (≥ 1/100 and < 1/10)	Uncommon (≥ 1/1000 and < 1/100)
Immune system disorders		Hypersensitivity reaction	
Metabolism and nutrition disorders		Increased weight	
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)		Breast discomfort
General disorders and administration site conditions		Injection site reaction	Bloating

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9. 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: not assigned

Protection against conception is based primarily upon an alteration of the cervical mucous. This alteration is present for the whole of the duration of action and prevents the ascent of the sperm into the uterine

cavity. Radioimmunological studies have shown that, during the first 5 to 7 weeks after injection, ovulation is suppressed as a result of the high plasma level of norethisterone. In addition, NUR-ISTERATE causes morphological changes in the endometrium which have the effect of rendering nidation of a fertilised egg difficult.

5.2. Pharmacokinetic properties

Absorption

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

Distribution

Plasma levels of norethisterone declined in two disposition phases with half-lives of 4 to 5 days and 15 to 20 days, respectively, which were due to a biphasic 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 C_4-C_5 double bond and the C_3 keto group. The majority of metabolites found in urine were present as conjugates, mainly as sulphates, which are expected to be inactive.

Norethisterone is partly metabolised to ethinylestradiol after intramuscular norethisterone enantate administration in humans. This conversion results in a systemic ethinylestradiol exposure corresponding to an oral equivalent dose of about 4 µg ethinylestradiol per day on average over 8 weeks and does not exceed a mean maximum oral equivalent dose of 20 µg ethinylestradiol per day. Mean oral equivalent doses per day are about 10 µg ethinylestradiol during the first 2 weeks after norethisterone enantate administration and decline to about 5 µg ethinylestradiol in the 3rd week and about 2 µg ethinylestradiol from the 5th week onwards. Based on these data systemic estrogen effects cannot be excluded. However, post-marketing experience indicates that the safety profile does not resemble that of combined hormonal contraceptives.

Elimination

Up to 85 % of the norethisterone enantate dose was 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 to 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 to 30 days was measured in urine between days 30 and 80 after IM administration of 200 mg ^{3}H-norethisterone enantate. Based on animal studies, retention in the body is not to be expected.
In plasma of women, 96 % of norethisterone is bound to proteins. The respective percentages bound to sex hormone binding globulin (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 will be expected after multiple administrations. A steady state will already be reached after the second administration.

Linearity/non-linearity

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

5.3. Preclinical safety data

None.

6. PHARMACEUTICAL PARTICUALRS

6.1. List of excipients

Benzyl benzoate
Castor oil for injection.

6.2. Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3. Shelf life

5 years

6.4. Special precautions for storage

Store at or below 30 °C. Protect from light.

6.5. Nature and content of container

Ampoule of 1 ml, glass type I.
Pack sizes: 1 x 1 mL and 100 x 1 ml.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
Isando
1609

8. REGISTRATION NUMBER

J/21.8.2/136

9. DATE OF FIRST AUTHORISATION

22 September 1976

10. DATE OF REVISION OF THE TEXT

14 April 2022