

romethane. Protect from light.

**USP 31** (Norethindrone Acetate). A white to creamy-white odourless crystalline powder. Practically insoluble in water; soluble 1 in 10 of alcohol, 1 in less than 1 of chloroform, 1 in 2 of dioxan, and 1 in 18 of ether.

### Norethisterone Enantate (BAN, PINNM)

Enantato de noretisterona; Noretisteron Enantat; Norethindrone Enanthate; Noréthistérone, Enantate de; Norethisterone Enanthate; Norethisterone Heptanoate; Norethisteroni Enantas. 17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one heptanoate.

Норэтистерона Энантат

$C_{27}H_{38}O_3 = 410.6$

CAS — 3836-23-5.

ATC — G03AC01; G03DC02.

ATC Vet — QG03AC01; QG03DC02.

Pharmacopoeias. In *Int*.

### Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059.

**Effects on the liver.** There were 6 cases of jaundice among 107 patients with breast cancer treated with high-dose norethisterone acetate;<sup>1</sup> the jaundice was reversible and of an obstructive type. A retrospective analysis<sup>2</sup> found that the use of norethisterone to prevent menstrual haemorrhage during the thrombocytopenic phase of allogeneic bone marrow transplantation was a significant risk factor for hepatic veno-occlusive disease.

- Langlands AO, Martin WMC. Jaundice associated with norethisterone-acetate treatment of breast cancer. *Lancet* 1975; **i**: 584-5.
- Häggglund H, *et al*. Norethisterone treatment, a major risk-factor for veno-occlusive disease in the liver after allogeneic bone marrow transplantation. *Blood* 1998; **92**: 4568-72.

**Porphyria.** Norethisterone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

**Pregnancy.** Abnormalities seen in the offspring of women given norethisterone during pregnancy (either alone or with ethinylestradiol) included: hypospadias,<sup>1</sup> masculinisation of female infants,<sup>2</sup> meningomyelocele or hydrocephalus,<sup>3</sup> and neonatal choreoathetosis associated with oral contraceptive use.<sup>4</sup> For reference to the fact that oral contraceptives have not generally been associated with teratogenicity, even when used inadvertently in pregnancy, see p.2067.

- Aarskog D. Clinical and cytogenetic studies in hypospadias. *Acta Paediatr Scand* 1970; (suppl 203): 1-62.
- Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; **172**: 1028-32.
- Gal I, *et al*. Hormonal pregnancy tests and congenital malformation. *Nature* 1967; **216**: 83.
- Profumo R, *et al*. Neonatal choreoathetosis following prenatal exposure to oral contraceptives. *Pediatrics* 1990; **86**: 648-9.

**Venous thromboembolism.** For mention that combined oral contraceptives containing older progestogens such as norethisterone appear to be associated with a lower incidence of venous thromboembolism than desogestrel- or gestodene-containing preparations, see p.2063.

### Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

### Pharmacokinetics

Norethisterone is absorbed from the gastrointestinal tract, undergoing first-pass hepatic metabolism, with peak plasma concentrations occurring 1 to 2 hours after an oral dose. It exhibits biphasic pharmacokinetics, an initial distribution phase is followed by a prolonged elimination phase with a half-life of about 8 hours or more. Norethisterone is highly protein bound; about 60% to albumin and 35% to sex hormone binding globulin. Use with an oestrogen increases the proportion bound to sex hormone binding globulin. It is metabolised in the liver with 50 to 80% of a dose being excreted in the urine and up to 40% appearing in the faeces.

Norethisterone acetate is rapidly hydrolysed to norethisterone, principally by intestinal tissue.

After intramuscular injection of norethisterone enantate peak concentrations of norethisterone in plasma are not attained for several days.

### Uses and Administration

Norethisterone and its acetate and enantate esters are progestogens (see Progesterone, p.2126) derived from

nortestosterone that have weak oestrogenic and androgenic properties. They are commonly used as **hormonal contraceptives** (see p.2069). Norethisterone and norethisterone acetate are both given orally. Typical daily doses are 350 micrograms for norethisterone and 600 micrograms for norethisterone acetate when used alone, or 0.5 to 1 mg for norethisterone and 1 to 1.5 mg for norethisterone acetate when used with an oestrogen. Norethisterone enantate is given by intramuscular injection; a dose of 200 mg provides contraception for 8 weeks. An intramuscular injection containing norethisterone enantate 50 mg with estradiol valerate 5 mg is given once each month.

Norethisterone and norethisterone acetate are used as the progestogen component of **menopausal HRT** (see p.2076). Typical regimens have included either continuous daily doses of norethisterone 700 micrograms or norethisterone acetate 0.5 to 1 mg, or cyclical regimens of norethisterone or norethisterone acetate 1 mg daily for 10 to 12 days of a 28-day cycle. Norethisterone acetate is also available as transdermal patches supplying 140, 170, or 250 micrograms in 24 hours, that are applied twice weekly for 2 weeks of a 4-week cycle; the lower strengths may also be applied twice weekly on a continuous basis.

Norethisterone and norethisterone acetate may be given orally, usually in divided doses, for the treatment of conditions such as **menorrhagia** (below) and **endometriosis** (p.2091). In menorrhagia (dysfunctional uterine bleeding), norethisterone is given in usual doses of 10 to 15 mg daily and norethisterone acetate in doses of 2.5 to 10 mg daily, in a cyclical regimen. In endometriosis the dosage of norethisterone is 10 to 25 mg daily and of norethisterone acetate 5 to 15 mg daily. Treatment of endometriosis is usually continuous for 4 to 9 months.

Norethisterone has been used in daily doses of up to 15 mg orally in a cyclical regimen in the treatment of **premenstrual syndrome** (p.2099).

In **breast cancer** (p.661) oral doses of up to 60 mg daily of norethisterone have been used.

**Administration in children.** Although unlicensed in the UK for use in children, the *BNFC* does include norethisterone for the management of delayed puberty (p.2079) in girls. It is added after 12 to 24 months of oestrogen therapy to establish a menstrual cycle and maintain sexual maturation, in an oral dose of 5 mg once daily for the last 7 days of a 28-day cycle.

**Menorrhagia.** Although cyclical norethisterone has been widely used for menorrhagia (p.2126), it is of limited efficacy during ovulatory cycles<sup>1</sup> being most effective for anovulatory bleeding, which occurs in a minority of women with menorrhagia.

- Lethaby A, *et al*. Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).

### Preparations

**BP 2008:** Estradiol and Norethisterone Acetate Tablets; Estradiol and Norethisterone Tablets; Norethisterone Tablets;

**USP 31:** Estradiol and Norethindrone Acetate Tablets; Norethindrone Acetate and Ethinyl Estradiol Tablets; Norethindrone Acetate Tablets; Norethindrone and Ethinyl Estradiol Tablets; Norethindrone and Mestranol Tablets; Norethindrone Tablets.

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Ginediot; Primolut-Nor; Selectan; **Austral.:** Locilan; Micronor; Noriday; Primolut N; **Austria:** Duokliman; Micronovum; Primolut-Nor; **Belg.:** Primolut-Nor; **Braz.:** Micronor; Norestin; Primolut-Nor; **Canad.:** Micronor; Norlutate; **Chile:** Primolut-Nor; **Cz.:** Primolut-Nor; **Denm.:** Mini-Pe; **Fin.:** Mini-Pik; Primolut N; Primolut-Nor; **Fr.:** Milligynon; Primolut-Nor; **Ger.:** Gestakadin; Noristerat; Primolut-Nor; **Hong Kong:** Primolut-Nor; **Hung.:** Norcolut; **India:** Cydoreg; Noristerat; Norlut; Primolut N; Syptin; **Indon.:** Anore; Norlut; Primolut N; **Regimen.:** **Ir.:** Noriday; Primolut N; **Israel:** Primolut-Nor; **Ital.:** Primolut-Nor; **Malaysia:** Depocin; Norcolut; Noriday; Noristerat; Primolut N; Sunolut; **Mex.:** Noristerat; Primolut-Nor; **Neth.:** Primolut N; **Norw.:** Concludag; Primolut N; **NZ:** Noriday; Primolut N; **Philipp.:** Noristerat; Primolut N; **Pol.:** Primolut-Nor; **Port.:** Primolut-Nor; **Rus.:** Primolut-Nor; **S. Afr.:** Micronovum; Norlutate; Primolut N; **Singapore:** Norcolut; Noristerat; Primolut N; **Spain:** Primolut-Nor; **Swed.:** Mini-Pe; Primolut-Nor; **Switz.:** Micronovum; Primolut N; **Thai.:** Noristerat; Primolut N; Steron; **Turk.:** Primolut N; **UK:** Micronor; Micronor HRT; Noriday; Noristerat; Primolut N; Utovlan; **USA:** Aygestin; Jolivet; Nor-QD; Ortho Micronor.

**Multi-ingredient:** **Arg.:** Activelle; Estalis; Estalis Sequi; Estracomb; Estrag-est; Evorel Conti; Evorel Sequi; Klogest; Mesigyna; Trial Combi; Trial Gest; Trial Pak; Trisequens; **Austral.:** Brevinor; Estalis Continuous; Estalis Sequi; Estracomb; Imprivol; Klogest; Kliovance; Norimin; Norinyl-I; Synphasic; Trisequens; **Austria:** Activelle; Estalis; Estalis Sequi; Estracomb; Fem-HRT; Klogest; Mericomb; Merigest; Novofem; Ovsymen; Penikliman; Primosiston; Trinovum; Trisequens; **Belg.:** Activelle; Estalis; Estracomb; Klogest; Minessin; Novofem; Ovsymen; Trinovum; Trisequens; **Braz.:**

Activelle; Biofimi; Cidovulon; Cliane; Estalis; Estalis SQ; Estracomb; Estrag-est; Gineane; Ginedic 50 Plus; Klogest; Megestran; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Primosiston; Suprema; System Conti; System Sequi; Trinovum; Trisequens; **Canad.:** Brevinor; Estalis; Estalis Sequi; Estracomb; Fem-HRT; Loestrin 1.5/30; Minestrin; Ortho 0.5/35; Ortho 1/35; Ortho 7/77; Ortho-Novum 1/50; Select 1/35; Synphasic; **Chile:** Activelle; Cliane; Enadiol Neta; Estracomb; Estrag-est; Ginefolin; Klogest; Mesigyna; Primosiston; Trisequens; **Cz.:** Activelle; Estalis; Estalis Sequi; Estrace Plus; Estrace-C; Estracomb; Estrag-est; Klogest; Mericomb; Menophas; Non-Ovlon; Novofem; Pausogest; Sequidut; System Conti; System Sequi; Triaklim; Trinovum; Trisequens; **Denm.:** Activelle; Econ; Estracomb; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Klogest; Novofem; Ostranorm; Trinorm; Trinovum; Trisequens; **Fin.:** Activelle; Estalis; Estalis Sekvens; Estracomb; Evorel Conti; Evorel Sequi; Klogest; Mericomb; Merigest; Novofem; Trisequens; **Fr.:** Activelle; Klogest; Miniphas; Novofemme; Ortho-Novum 1/35; Triella; Trisequens; **Ger.:** Activelle; Clonara; Conceplan M; Estalis Sequi; Evorel Conti; Evorel Sequi; Klogest; Mericomb; Merigest; Novofem; Trisequens; **Hong Kong:** Activelle; Brevinor; Estracomb; Klogest; Mesigyna; Norinyl-I; Novofem; Synphasic; Trinovum; Trisequens; **Gr.:** Activelle; Estracomb TT5; Klogest; System Conti; System Sequi; Trisequens; **Israel:** Activelle; Brevinor; Estracomb; Estrag-est; Estrag-est; Evorel Conti; Evorel Sequi; Klogest; Meno-Nett; Novofem; Trisequens; **Ital.:** Activelle; Estalis Sequi; Estracomb; Klogest; Trisequens; **Jpn.:** Ortho 7/77; **Malaysia:** Activelle; Klogest; **Mex.:** Cliane; Estalis; Estracomb; Evorel Conti; Mesigyna; Norace; Norinyl; Nostidin; Ortho-Novum 1/35; Ortho-Novum; **Neth.:** Activelle; Estalis; Estalis Sequi; Estracomb; Klogest; Modicon; Necon; Novofem; Trinovum; Trisequens; **Norw.:** Activelle; Estalis; Estalis Sekvens; Klogest; Novofem; Synfase; Trisequens; **NZ:** Brevinor; Cliane; Estrapak; Klogest; Klogest; Norimin; Norinyl-I; Synphasic; Trisequens; **Philipp.:** Klogest; Micropil; **Pol.:** Activelle; Estalis; Estalis Sequi; Estracomb; Klogest; Novofem; System Conti; System Sequi; Trinovum; Trisequens; **Port.:** Activelle; Estalis; Estalis Sequi; Estracomb; Klogest; Novofem; Trisequens; **Rus.:** Non-Ovlon (Нон-овлон); Pausogest (Пайзогест); Triaklim (Триаклим); Trisequens (Трисеквенс); **S. Afr.:** Activelle; Brevinor; Estracomb; Estro-Pause N; Evorel Conti; Evorel Sequi; Klogest; Norinyl-I/28; Novofem; Trinovum; Trisequens; **Singapore:** Activelle; Estracomb; Klogest; Trisequens; **Spain:** Absorlent Plus; Activelle; Duofemme; Endomina Plus; Estalis; Estalis Sequi; Estracomb; Merigest; Merigest Sequi; Trisequens; **Swed.:** Activelle; Estalis; Estalis Sekvens; Estracomb; Evorel Micronor; Femanor; Femasekvens; Klogest; Novofem; Ortho-Nett; Novum; Synfase; Trinovum; Trisequens; **Switz.:** Activelle; Estalis; Estalis Sequi; Estracomb; Estrag-est; Klogest N; Mericomb; Merigest; Novofem; Ovsymen; Primosiston; System Conti; System Sequi; Trinovum; Trisequens; **Thai.:** Activelle; Anamari; **Turk.:** Activelle; Estracomb; Klogest; Mesigyna; Trisequens; **UK:** Binovum; Brevinor; Climagest; Climesse; Clinor-ette; Elleste Duet Conti; Elleste-Duet; Estracomb; Estrapak; Evorel Conti; Evorel Pak; Evorel Sequi; FemTab Continuous; Klogest; Kliovance; Loestrin; Norimin; Norinyl-I; Novofem; Nuvelle Continuous; Ovsymen; Synphasic; Trinovum; Trisequens; **USA:** Activella; Aranelle; Balziva; Brevicon; CombiPatch; Estrostep Fe; Estrostep; Femcon Fe; Fem-HRT; Junel Fe; Lee-na; Loestrin; Loestrin Fe; Modicon; Necon 1/50; Necon 10/11; Necon 0.5/35; 1/35; NEE 1/35; Norinyl I + 35; Norinyl I + 50; Ortho-Novum 1/35; Ortho-Novum 1/50; Ortho-Novum 10/11; Ortho-Novum 7/77; Ovcon 35; Ovcon 50; Tilia Fe; Tri-Legest; Tri-Norinyl; Zenthen; **Venez.:** Cliane; Estracomb; Estrag-est; Mesigyna; Primosiston;.

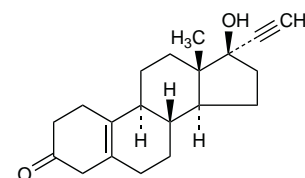
### Noretynodrel (BAN, rINN)

Norethynodrel (*USAN*); Noretynodrel; Noretynodreli; Norétyndrel; Noretynodrelum; NSC-15432; SC-4642. 17β-Hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

Норэтинодрел

$C_{20}H_{26}O_2 = 298.4$

CAS — 68-23-5.



### Pharmacopoeias. In *US*.

**USP 31** (Norethynodrel). A white or practically white, odourless, crystalline powder. Very slightly soluble in water and in petroleum spirit; sparingly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

### Profile

Noretynodrel is a progestogen (see Progesterone, p.2125) structurally related to norethisterone that has been given orally with an oestrogen such as mestranol for the treatment of various menstrual disorders and endometriosis.

**Breast feeding.** About 1% of an oral dose of radiolabelled noretynodrel was detected in breast milk in a study of 4 women.<sup>1</sup> No adverse effects have been seen in breast-fed infants of mothers given noretynodrel, and the American Academy of Pediatrics considers<sup>2</sup> that it is therefore usually compatible with breast feeding.

- Laumas KR, *et al*. Radioactivity in the breast milk of lactating women after oral administration of H-noretynodrel. *Am J Obstet Gynecol* 1967; **98**: 411-3.
- American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776-89. Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 27/06/08)