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 *(BANM, pINNM)*

Enantato de noretisterona; Norestisteron 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;[1] the jaundice was reversible and of an obstructive type. A retrospective analysis[2] 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.

1. Langlands AO, Martin WMC. Jaundice associated with norethisterone-acetate treatment of breast cancer. *Lancet* 1975; **i:** 584–5.
2. Hägglund 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,[1] masculinisation of female infants,[2] meningomyelocele or hydrocephalus,[3] and neonatal choreoathetosis associated with oral contraceptive use.[4] For reference to the fact that oral contraceptives have not generally been associated with teratogenicity, even when used inadvertently in pregnancy, see p.2067.

1. Aarskog D. Clinical and cytogenetic studies in hypospadias. *Acta Paediatr Scand* 1970; (suppl 203): 1–62.
2. Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; **172:** 1028–32.
3. Gal I, *et al.* Hormonal pregnancy tests and congenital malformation. *Nature* 1967; **216:** 83.
4. 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[1] being most effective for anovulatory bleeding, which occurs in a minority of women with menorrhagia.

1. 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.: Ginediol; 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-Pill; Primolut N; Primolut-Nor; ***Fr.:*** Milligynon; Primolut-Nor; ***Ger.:*** Gestakadin; Noristerat; Primolut-Nor; Sovel†; ***Gr.:*** Fortilut; Primolut-Nor; ***Hong Kong:*** Norcolut; Primolut N; ***Hung.:*** Norcolut; ***India:*** Cycloreg; Noristerat; Norlut; Primolut N; Styptin; ***Indon.:*** Anore; Norelut; Primolut N; Regumen; ***Irl.:*** Noriday; Primolut N; ***Israel:*** Primolut-Nor; ***Ital.:*** Primolut-Nor; ***Malaysia:*** Depocon; Norcolut; Noriday; Noristerat; Primolut N; Sunolut; Trisequens†; ***Mex.:*** Noristerat; Primolut-Nor; ***Neth.:*** Primolut N; ***Norw.:*** Conludag; Primolut N; ***NZ:*** Noriday; Primolut N; ***Philipp.:*** Noristerat; Primolut N; ***Pol.:*** Primolut-Nor; ***Port.:*** Primolut-Nor; ***Rus.:*** Primolut-Nor (Примолют-нор); ***S.Afr.:*** Micronovum; Nur-Isterate; 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; Jolivette; Nor-QD; Ortho Micronor.

Multi-ingredient: ***Arg.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Estragest; Evorel Conti; Evorel Sequi; Kliogest; Mesigyna; Trial Combi; Trial Gest; Trial Pack†; Trisequens; ***Austral.:*** Brevinor; Estalis Continuous; Estalis Sequi; Estracombi; Improvil; Kliogest; Kliovance; Norimin; Norinyl-1; Synphasic; Trisequens; ***Austria:*** Activelle; Estalis; Estalis Sequens; Estracomb; Fem-HRT†; Kliogest; Mericomb; Merigest; Novofem; Ovysmen; Perikliman; Primosiston; Trinovum; Trisequens; ***Belg.:*** Activelle; Estalis; Estracombi; Kliogest; Minestril†; Novofem; Ovysmen; Trinovum; Trisequens; ***Braz.:*** Activelle; Biofim†; Ciclovulon; Cliane; Estalis; Estalis SQ; Estracomb†; Estragest; Gineane; Ginedisc 50 Plus†; Kliogest; Megestran†; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Primosiston; Suprema; Systen Conti; Systen Sequi; Trinovum†; Trisequens; ***Canad.:*** Brevicon; Estalis; Estalis Sequi; Estracomb; FemHRT; Loestrin 1.5/30; Minestrin; Ortho 0.5/35; Ortho 1/35; Ortho 7/7/7; Ortho-Novum 1/50†; Select 1/35; Synphasic; ***Chile:*** Activelle; Cliane; Enadiol Neta; Estracomb; Estragest; Ginefolin; Kliogest; Mesigyna; Primosiston; Trisequens; ***Cz.:*** Activelle; Estalis; Estalis Sequi; Estrace Plus†; Estrace-C†; Estracomb†; Estragest†; Kliane; Kliogest; Menophase†; Non-Ovlon†; Novofem; Pausogest; Sequidot; Systen Conti; Systen Sequi; Triaklim†; Trinovum; Trisequens; ***Denm.:*** Activelle; Econ†; Estracomb; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Kliogest; Novofem; Ostranorm†; Trinorm†; Trinovum; Trisekvens; ***Fin.:*** Activelle; Estalis; Estalis Sekvens; Estracomb†; Evorel Conti; Evorel Sequi; Kliogest; Mericomb; Merigest; Novofem; Trisekvens; ***Fr.:*** Activelle; Kliogest; Miniphase; Novofemme; Ortho-Novum 1/35; Triella; Trisequens; ***Ger.:*** Activelle; Clionara; Conceplan M; Estalis Sequi; Estracomb†; Estragest; Eve; Gynamon; Kliogest N; Mericomb; Merigest; Non-Ovlon†; Nora-ratiopharm†; Novofem; Ostro-Primolut†; Ovysmen†; Primosiston†; Prosiston†; Sequostat†; Sinovula†; Synphasec; Trinovum; Trisequens; ***Gr.:*** Activelle†; Estalis; Estracomb TTS; Kliogest; Systen Conti; Systen Sequi; Trisequens; ***Hong Kong:*** Activelle; Brevinor; Estracomb; Kliogest; Norimin†; Norinyl-1; Novofem; Synphase†; Trinovum†; Trisequens; ***Hung.:*** Activelle; Estracomb; Estragest; Kliogest; Pausogest; Trialklim; Trisequens; Tulita; ***Irl.:*** Activelle; Brevinor; Estalis; Estalis Sequi; Estracombi; Estrapak†; Evorel Conti; Kliogest; Novofem; Trisequens; ***Israel:*** Activelle; Evorel Conti; Evorel Sequi; Kliogest; Meno-Net†; Novofem; Trisequens; ***Ital.:*** Activelle; Estalis Sequi; Estracomb; Kliogest; Trisequens; ***Jpn:*** Ortho 777; ***Malaysia:*** Activelle; Kliogest†; ***Mex.:*** Cliane; Estalis; Estracomb; Evorel Conti; Mesigyna; Norace; Norinyl; Nostidyn; Ortho-Novum 1/35; Ortho-Novum†; ***Neth.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Kliogest; Modicon; Neocon; Novofem; Trinovum; Trisequens; ***Norw.:*** Activelle; Estalis; Estalis Sekvens; Kliogest; Novofem; Synfase; Trisekvens; ***NZ:*** Brevinor; Cliane; Estrapak†; Kliogest; Kliovance; Norimin; Norinyl-1; Synphasic; Trisequens; ***Philipp.:*** Kliogest; Micropil; ***Pol.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Kliogest; Novofem; Systen Conti; Systen Sequi; Trinovum; Trisequens; ***Port.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Kliogest; Novofem; Trisequens; ***Rus.:*** Non-Ovlon (Нон-овлон); Pausogest (Пауэогест); Triaklim (Триаклим); Trisequens (Трисеквенс); ***S.Afr.:*** Activelle; Brevinor†; Estracombi; Estro-Pause N; Evorel Conti; Evorel Sequi; Kliogest; Norinyl-1/28; Novofem; Trinovum; Trisequens; ***Singapore:*** Activelle; Estracomb; Kliogest; 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; Kliogest; Novofem; Orthonett Novum; Synfase; Trinovum; Trisekvens; ***Switz.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Estragest; Kliogest N; Mericomb; Merigest; Novofem; Ovysmen; Primosiston; Systen Conti; Systen Sequi; Trinovum; Trisequens; ***Thai.:*** Activelle; Anamai†; ***Turk.:*** Activelle; Estracombi; Kliogest; Mesigyna; Trisequens; ***UK:*** Binovum; Brevinor; Climagest; Climesse; Clinorette; Elleste Duet Conti; Elleste-Duet; Estracombi; Estrapak†; Evorel Conti; Evorel Pak†; Evorel Sequi; FemTab Continuous†; Kliofem; Kliovance; Loestrin; Norimin; Norinyl-1; Novofem; Nuvelle Continuous; Ovysmen; Synphase; Trinovum; Trisequens; ***USA:*** Activella; Aranelle; Balziva; Brevicon; CombiPatch; Estrostep Fe; Estrostep†; Femcon Fe; FemHRT; Junel Fe; Leena; Loestrin; Loestrin Fe; Modicon; Necon 1/50; Necon 10/11; Necon 0.5/35, 1/35; NEE 1/35; Norinyl 1 + 35; Norinyl 1 + 50; Ortho-Novum 1/35; Ortho-Novum 1/50; Ortho-Novum 10/11; Ortho-Novum 7/7/7; Ovcon 35; Ovcon 50; Tilia Fe; Tri-Legest; Tri-Norinyl; Zenchent; ***Venez.:*** Cliane; Estracomb†; Estragest; Mesigyna; Primosiston†.

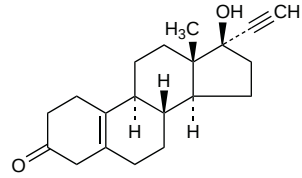
Noretynodrel *(BAN, rINN)*

Norethynodrel *(USAN)*; Noretinodrel; Noretynodreeli; Norétynodrel; 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.[1] No adverse effects have been seen in breast-fed infants of mothers given noretynodrel, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Laumas KR, *et al.* Radioactivity in the breast milk of lactating women after oral administration of H-norethynodrel. *Am J Obstet Gynecol* 1967; **98:** 411–3.
2. 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)

Porphyria. Noretynodrel is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Pregnancy. A woman given noretynodrel during pregnancy to prevent threatened miscarriage gave birth to a female infant showing signs of masculinisation.[1]

1. Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; **172:** 1028–32.

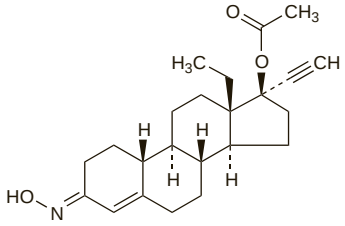
Norgestimate *(BAN, USAN, rINN)*

D-138; Dexnorgestrel Acetime; Norgestimaatti; Norgestimat; Norgestimato; Norgestimatum; ORF-10131; RWJ-10131. 13β-Ethyl-3-hydroxyimino-18,19-dinor-17α-pregn-4-en-20-yn-17β-yl acetate.

Норгестимат

$C_{23}H_{31}NO_3$ = 369.5.

CAS — 35189-28-7.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Norgestimate). A white or almost white powder. Practically insoluble in water; freely soluble in dichloromethane; soluble in acetone.

USP 31 (Norgestimate). A mixture of (*E*)- and (*Z*)-isomers having a ratio of (*E*)- to (*Z*)-isomer between 1.27 and 1.78. A white to pale yellow powder. Insoluble in water; sparingly soluble in acetonitrile; freely to very soluble in dichloromethane.

Profile

Norgestimate is a progestogen (see Progesterone, p.2125) structurally related to levonorgestrel (to which it is partly metabolised) that is used as the progestogenic component of combined oral contraceptives (see p.2058) and in menopausal HRT (see p.2071). A typical daily dose is 250 micrograms in monophasic contraceptive preparations, and 180 to 250 micrograms in triphasic preparations. For HRT, a regimen of estradiol daily for 3 days followed by estradiol with norgestimate 90 micrograms daily for 3 days is used; this 6-day cycle is repeated continuously without interruption.

Preparations

USP 31: Norgestimate and Ethinyl Estradiol Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Cilest; Prefest; Tridette; ***Austria:*** Cileste; Tri-Cilest; Vivelle; ***Belg.:*** Cilest; ***Braz.:*** Prefest; ***Canad.:*** Cyclen; Tri-Cyclen; ***Chile:*** Mactex; Neofam; Orlon; Tri-Mactex; Trifas†; ***Cz.:*** Cilest; Pramino; ***Denm.:*** Cilest; ***Fin.:*** Cilest; ***Fr.:*** Cilest; Effiprev; Triafemi; TriCilest; ***Ger.:*** Cilest; Pramino; ***Hung.:*** Cilest; ***Irl.:*** Cilest; ***Israel:*** Ortho Cyclen; ***Mex.:*** Cilest; Prefest; ***Neth.:*** Cilest; ***Pol.:*** Cilest; ***Rus.:*** Cilest (Силест); ***S.Afr.:*** Cilest; Prefesta; TriCilest; ***Swed.:*** Cilest; ***Switz.:*** Cilest; ***Thai.:*** Cilest; Tri-Cilest; ***UK:*** Cilest; ***USA:*** Ortho Cyclen; Ortho Tri-Cyclen; Prefest; Previfem; Sprintec; Tri-Previfem; Tri-Sprintec; TriNessa; ***Venez.:*** Ortrel.

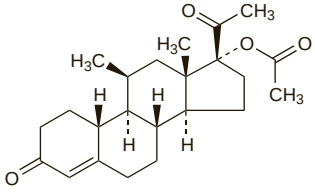
Norgestomet *(BAN, USAN, rINN)*

Norgestometum; SC-21009. 11β-Methyl-3,20-dioxo-19-nor-pregn-4-en-17α-yl acetate.

Норгестомет

$C_{23}H_{32}O_4$ = 372.5.

CAS — 25092-41-5.



Profile

Norgestomet is a progestogen (see Progesterone, p.2125) used in veterinary medicine with estradiol.

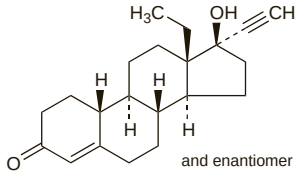
Norgestrel *(BAN, USAN, rINN)*

Norgestreeli; *dl*-Norgestrel; DL-Norgestrel; Norgestrelis; Norgestrelum; Norgesztrel; Wy-3707. (±)-13-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

Норгестрел

$C_{21}H_{28}O_2$ = 312.4.

CAS — 6533-00-2.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Norgestrel). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

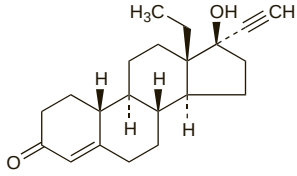
USP 31 (Norgestrel). A white or practically white, practically odourless crystalline powder. Insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform.

Levonorgestrel *(BAN, USAN, rINN)*

Levonorgestreeli; Lévonorgestrel; Levonorgestrelis; Levonorgestrelum; Levonorgesztrel; D-Norgestrel; Wy-5104. (–)-13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

Левоноргестрел

CAS — 797-63-7.
ATC — G03AC03.
ATC Vet — QG03AC03.



NOTE. The name Dexnorgestrel has also been used.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Levonorgestrel). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Levonorgestrel). A white or practically white, odourless powder. Practically insoluble in water; slightly soluble in alcohol; soluble in chloroform. Protect from light.

Adverse Effects and Precautions

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

Incidence of adverse effects. After the introduction of levonorgestrel in a subdermal implant formulation in February 1991, the US FDA had received about 5800 reports of adverse effects as of December 1993 (out of an estimated 891 000 implants distributed).[1] Serious adverse effects associated with the implant included 24 cases of infection related to insertion of the implant, 15 cases of stroke and 39 of benign intracranial hypertension, 3 cases of thrombocytopenic purpura and 6 of thrombocytopenia (1 fatal). None of the reporting rates for these disorders exceeded the expected rate in this population. In a 5-year cohort study[2] of more than 16 000 women who received either a levonorgestrel implant or an IUD (not progestogen-releasing), or underwent sterilisation, there was no significant risk of major morbidity associated with the implant, although there were moderately elevated risks of gallbladder disease and raised blood pressure in current users.

1. Wysowski DK, Green L. Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. *Obstet Gynecol* 1995; **85:** 538–42.
2. Meirik O, *et al.* Safety and efficacy of levonorgestrel implant, intrauterine device, and sterilization. *Obstet Gynecol* 2001; **97:** 539–47.

Benign intracranial hypertension. Intracranial hypertension, presenting as headaches, vomiting, and visual obscuration associated with florid bilateral papilloedema developed in 2 patients 4 to 5 months after subdermal implantation of levonorgestrel.[1] Despite a further 56 cases reported to various drug monitoring centres, and 70 cases known to the manufacturers,[2] it remained unclear whether the drug actually caused intracranial hypertension, but removal of implants was recommended in patients in whom intracranial pressure increased.

1. Alder JB, *et al.* Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995; **332:** 1720–1.
2. Weber ME, *et al.* Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995; **332:** 1721.

Breast feeding. Levonorgestrel was detected in breast milk and the circulation of breast-fed infants during the use of either a levonorgestrel IUD, subcutaneous implant, or progestogen-only oral contraceptive.[1] A review[2] of studies of a levonorgestrel implant used during lactation concluded that it did not adversely affect the duration of lactation, infant growth or development. Further studies of a levonorgestrel IUD[3] and implant[4] also found no adverse effect on lactation or infant growth. The implant study[4] did find an increased incidence of mild respiratory, skin, and eye diseases in infants in the first year of life, but the possibility of bias or chance could not be excluded. The American Academy of Pediatrics considers that levonorgestrel is usually compatible with breast feeding.[5] Progestogen-only contraceptives should not be started until several weeks after birth if the woman is breast feeding (see Breast Feeding under Hormonal Contraceptives, p.2066).

In a pharmacokinetic study[6] using a single oral dose of levonorgestrel 1.5 mg, the drug concentration peaked between 2 and 4 hours in breast milk and then fell rapidly. The authors suggested that breast-feeding women who are given this dose of levonorgestrel for emergency contraception should be advised to breast feed immediately before the dose, then discard milk for at least 8 hours but not more than 24 hours.

1. Shikary ZK, *et al.* Transfer of levonorgestrel (LNG) administered through different drug delivery systems from the maternal circulation into the newborn infant's circulation via breast milk. *Contraception* 1987; **35:** 477–86.
2. Díaz S. Contraceptive implants and lactation. *Contraception* 2002; **65:** 39–46.
3. Shaamash AH, *et al.* A comparative study of the levonorgestrel-releasing intrauterine system Mirena versus the copper T380A intrauterine device during lactation: breast-feeding performance, infant growth and infant development. *Contraception* 2005; **72:** 346–51.
4. Schiappacasse V, *et al.* Health and growth of infants breastfed by Norplant contraceptive implants users: a six-year follow-up study. *Contraception* 2002; **66:** 57–65.
5. 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)
6. Gainer E, *et al.* Levonorgestrel pharmacokinetics in plasma and milk of lactating women who take 1.5 mg for emergency contraception. *Hum Reprod* 2007; **22:** 1578–84.

Effects on the blood. Studies[1-3] of women who had been given different levonorgestrel subcutaneous implants found that over 5 years there were various changes in blood clotting factors, fibrinolytic activity, and platelet number and aggregation, some of which persisted even 6 months after removal of the implants. However, these haemostatic changes did not result in activation of the coagulation system or a state of hypercoagulation.

1. Singh K, *et al.* Evaluation of hemostatic function following Norplant implant removal. *Adv Contracept* 1993; **9:** 49–58.
2. Singh K, *et al.* Evaluation of hemostatic function following Norplant-2 rods removal. *Adv Contracept* 1993; **9:** 241–50.
3. Koh SCL, *et al.* A prospective study on the effects of reformulated 2-rod Norplant implant on haemostasis after five years of use. *J Obstet Gynaecol Res* 1999; **25:** 177–83.

Effects on carbohydrate metabolism. For a mention that levonorgestrel has been reported to be the most potent progestogen associated with hyperinsulinaemia when used as a combined oral contraceptive, see p.2061.

Glucocorticoid effects. Reference to the minimal suppressive effect of subdermal levonorgestrel on adrenal function.[1]

1. Toppozada MK, *et al.* Effect of Norplant implants on the pituitary-adrenal axis function and reserve capacity. *Contraception* 1997; **55:** 7–10.

Myasthenia gravis. Myasthenia gravis occurring after insertion of a levonorgestrel implant improved on removal of the implant.[1]

1. Brittain J, Lange LS. Myasthenia gravis and levonorgestrel implant. *Lancet* 1995; **346:** 1556.

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

Pregnancy. Adverse effects in infants whose mothers had received oral contraceptives containing norgestrel during early pregnancy have included tracheo-oesophageal fistula in one infant[1] and inoperable hepatoblastoma in another.[2] However, many epidemiological studies have failed to show any association between fetal malformations and oral contraceptives, even when used inadvertently during pregnancy, see p.2067.

1. Frost O. Tracheo-oesophageal fistula associated with hormonal contraception during pregnancy. *BMJ* 1976; **2:** 978.
2. Otten J, *et al.* Hepatoblastoma in an infant after contraceptive intake during pregnancy. *N Engl J Med* 1977; **297:** 222.