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.

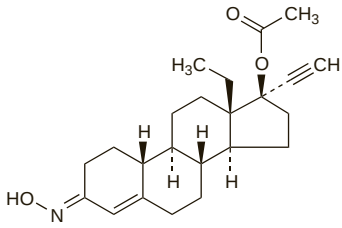
Norgestimate *(BAN, USAN, rINN)*

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; TriCilest; 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; TriCilest; ***UK:*** Cilest; ***USA:*** Ortho Cyclen; Ortho Tri-Cyclen; Prefest; Previfem; Sprintec; Tri-Previfem; Tri-Sprintec; TriNessa; ***Venez.:*** Ortrel.

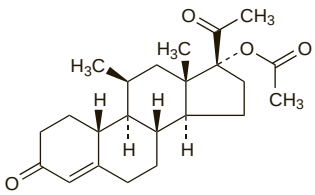
Norgestomet *(BAN, USAN, rINN)*

Norgestometum; SC-21009. 11β-Methyl-3,20-dioxo-19-norpregn-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.

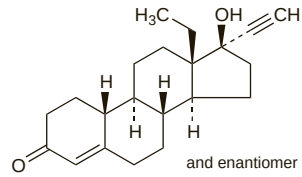
Norgestrel *(BAN, USAN, rINN)*

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.

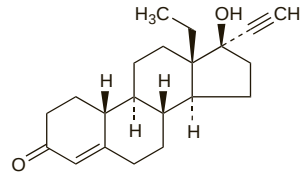
USP 31 (Norgestrel). A white or practically white, practically odourless crystalline powder. Insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform.

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.