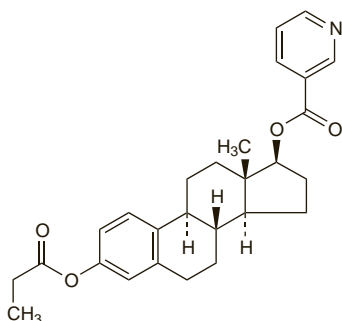


Estrapronicate (rINN)

Estrapronicato; Estrapronicatum. Oestradiol 17-nicotinate 3-propionate.

Эстрапроникат
 $C_{27}H_{31}NO_4 = 433.5$.
 CAS — 4140-20-9.

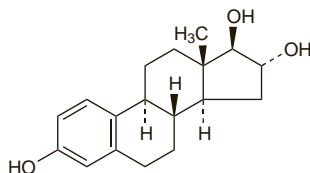
**Profile**

Estrapronicate is a derivative of estradiol (p.2097) with nicotinic acid. It has been used as an ingredient of a combined preparation with anabolic steroid and a progestogen for osteoporosis.

Estriol (BAN, rINN)

Estrioli; Estriolis; Estriolum; Follicular Hormone Hydrate; Oestriol; Östriol; Östriol; Theelol. Estra-1,3,5(10)-triene-3,16 α ,17 β -triol.

Эстриол
 $C_{18}H_{24}O_3 = 288.4$.
 CAS — 50-27-1.
 ATC — G03CA04.
 ATC Vet — QG03CA04; QG03CC06.



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

Ph. Eur. 6.2 (Estriol). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol.
USP 31 (Estriol). A white or practically white, odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, in dioxan, in ether, and in vegetable oils. Store in airtight containers.

Estriol Sodium Succinate (BAN, rINN)

Estriol, Succinate Sodique d'; Estrioli Natrii Succinas; Oestriol Sodium Succinate; Succinato sódico de estriol. Disodium 3-hydroxyestra-1,3,5(10)-triene-16 α ,17 β -diyl disuccinate.

Эстриола Натрия Сукцинат
 $C_{26}H_{30}Na_2O_9 = 532.5$.
 CAS — 113-22-4.
 ATC — G03CA04.
 ATC Vet — QG03CA04.

Estriol Succinate (BAN, rINN)

Estriol, Succinate d'; Estrioli Succinas; Estriolisuksinaatti; Estriol-succinat; Oestriol Succinate; Succinato de estriol. 3-Hydroxyestra-1,3,5(10)-triene-16 α ,17 β -diyl di(hydrogen succinate).

Эстриола Сукцинат
 $C_{26}H_{32}O_9 = 488.5$.
 CAS — 514-68-1.
 ATC — G03CA04.
 ATC Vet — QG03CA04.

Profile

Estriol is a naturally occurring oestrogen with actions and uses similar to those described for estradiol (p.2097). It is claimed to have only a mild proliferative effect on the endometrium.

It is used for menopausal HRT (p.2071). When oestrogens are given to women with a uterus, a progestogen is required, particularly if used long term. For short-term treatment, oral doses of estriol have been 0.5 to 3 mg daily given for one month followed by 0.5 to 1 mg daily. Estriol has also been given with other natural oestrogens such as estradiol and estrone (see below); usual doses of estriol have ranged from about 0.25 to 2 mg daily. Estriol may be used intravaginally for the short-term treatment of

menopausal atrophic vaginitis and kraurosis vulvae. A dose of 500 micrograms may be given as a 0.01% or 0.1% cream or as a pessary; initial treatment may be given once daily, then reduced to twice each week.

Estriol has also been given orally for infertility (p.2080) caused by poor cervical penetration, in a dose of 0.25 to 1 mg daily on days 6 to 15 of the menstrual cycle.

Estriol succinate has also been given orally in the treatment of menopausal disorders. The sodium succinate salt has been used parenterally in the treatment of haemorrhage and thrombocytopenia.

Preparations

BP 2008: Estriol Cream.

Proprietary Preparations (details are given in Part 3)

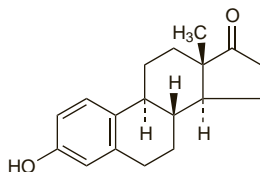
Arg.: Colpoestriol; Orgeestriol; **Austral.:** Ovestin; **Austria:** Ortho-Gynest; Ovestin; Styntanon; **Belg.:** Aacifemine; Ortho-Gynest; **Braz.:** Estriopax; Hormocervix; Hormoniol; Ovestrin; Styntanon; **Chile:** Ovestin; Sinapause; Vacidox; **Cz.:** Ortho-Gynest; Ovestin; **Denm.:** Ovestin; **Fin.:** Ovestin; Pausanol; **Fr.:** Gydrelle; Physiogine; Trophicreme; **Ger.:** Cordes Estriol; Gynasint; Oekolp; Oestro-Gynaedron M; Ortho-Gynest; Ovestin; Sinapause E; Xaprio; **Gr.:** Ovestin; **Hong Kong:** Ovestint; **Hung.:** Estrokad; Ortho-Gynest; Ovestin; **India:** Evalon; **Indon.:** Ovestin; **Irl.:** Ortho-Gynest; **Israel:** Ortho-Gynest; Ovestin; **Ital.:** Colpogyn; Ortho Gynest Depot; Ovestin; Trofogin; **Jpn.:** Estriol; **Mex.:** Ortho-Gynest; Ovestin; Sinapause; **Neth.:** Synapause-E; **Norw.:** Ovesterin; **NZ:** Ovestin; **Philipp.:** Ovestin; **Pol.:** Oekolp; Ortho-Gynest; Ovestin; **Port.:** Ovestin; Pausigin; Synapausa; **Rus.:** Ovestin (Овэстин); **S.Afr.:** Synapause; **Spain:** Ovestinon; **Swed.:** Ovesterin; **Switz.:** Oestro-Gynaedron Nouveau; Ortho-Gynest; Ovestin; **Thai:** Ovestint; **Turk.:** Estrolem; Ovestin; **UK:** Ortho-Gynest; Ovestin; **Venez.:** Ortho-Gynest; Ovestin.

Multi-ingredient: **Arg.:** Tropivag Plus; **Austria:** Gynoflor; **Belg.:** Gynoflor; **Cz.:** Cyclo-Menorette; CycloOstrogynal; Gynoflor; **Fr.:** Florgynal; Trophigil; **Ger.:** Cyclo-Menorette; CycloOstrogynal; Gynoflor; NeoOstrogynal; Oestrugol N; **Hong Kong:** Hormonin; **Hung.:** Cyclo-Menorette; Gynoflor; **Port.:** Gynoflor; **Switz.:** Gynoflor; **Turk.:** Gynoflor; **UK:** Hormonin.

Estrone (BAN, rINN)

Estron; Estrona; Estroni; Estronum; Folliculina; Follicular Hormone; Folliculin; Kethydroxyoestrin; Oestrone; Östron. 3-Hydroxyestra-1,3,5(10)-trien-17-one.

Эстрон
 $C_{18}H_{22}O_2 = 270.4$.
 CAS — 53-16-7.
 ATC — G03CA07.
 ATC Vet — QG03CA07; QG03CC04.



Pharmacopoeias. In *US*.

USP 31 (Estrone). Odourless, small white crystals or white to creamy-white crystalline powder. Practically insoluble in water; soluble 1 in 250 of alcohol and 1 in 110 of chloroform at 15°; soluble 1 in 50 of boiling alcohol, 1 in 33 of boiling acetone, 1 in 145 of boiling benzene, and 1 in 80 of boiling chloroform; soluble 1 in 50 of acetone at 50°; soluble in dioxan and in vegetable oils; slightly soluble in solutions of fixed alkali hydroxides. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Estrone is a naturally occurring oestrogen with actions and uses similar to those described for estradiol (see p.2097).

For menopausal HRT (see p.2071) estrone has been given orally at a dose of 1.4 to 2.8 mg daily in a cyclical or continuous regimen, as a combination product with estradiol and estriol (see above). Estrone has also been given by intramuscular injection in oily solutions and aqueous suspensions. When used specifically for menopausal atrophic vaginitis, estrone has been given vaginally. If used in women with a uterus, estrone by any route should be given with a progestogen.

Preparations

USP 31: Estrone Injectable Suspension; Estrone Injection.

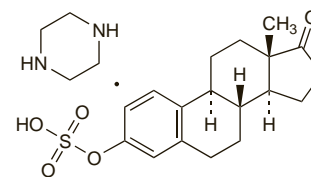
Proprietary Preparations (details are given in Part 3)
USA: Kestrone.

Multi-ingredient: **Braz.:** Gineburnot; **Fin.:** Senikolp; **Fr.:** Synergyn; **Hong Kong:** Hormonin; **Spain:** Cicatral; Grietalgen; Grietalgen Hydrocort; **Thai.:** Metharmon-F; **Turk.:** Synergyn; **UK:** Hormonin.

Estropipate (BAN)

Estropipato; Piperazine Estrone Sulfate; Piperazine Oestrone Sulphate. Piperazine 17-oxoestra-1,3,5(10)-trien-3-yl hydrogen sulphate.

Эстропионат
 $C_{18}H_{22}O_5S.C_4H_{10}N_2 = 436.6$.
 CAS — 7280-37-7.



Pharmacopoeias. In *Br.* and *US*.

BP 2008 (Estropipate). A white or almost white crystalline powder. Very slightly soluble in water, in alcohol, in chloroform, and in ether.

USP 31 (Estropipate). A white to yellowish-white fine crystalline powder, odourless or may have a slight odour. Very slightly soluble in water, in alcohol, in chloroform, and in ether; soluble 1 in 500 of warm alcohol; soluble in warm water. Store in airtight containers.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). See also under Hormone Replacement Therapy, p.2071.

Interactions

See under Hormone Replacement Therapy, p.2076.

Uses and Administration

Estropipate is a semisynthetic conjugate of estrone with piperazine that is used for menopausal HRT (see p.2076). Its action is due to estrone (see above) to which it is hydrolysed in the body.

Estropipate is given orally for the short-term treatment of menopausal symptoms; suggested doses have ranged from 0.75 to 3 mg daily, given cyclically or continuously; doses up to 6 mg daily have also been given cyclically. When used longer term for the prevention of postmenopausal osteoporosis a daily dose of 0.75 or 1.5 mg is given cyclically or continuously. In women with a uterus estropipate should be used with a progestogen. Estropipate has also been used short term for menopausal atrophic vaginitis as a vaginal cream containing 0.15%; 2 to 4 g of cream is applied daily. It is also given orally in the treatment of female hypogonadism, castration, and primary ovarian failure in doses of 1.5 to 3 mg daily, in a cyclical regimen; higher doses of up to 9 mg daily given cyclically have also been used.

Preparations

BP 2008: Estropipate Tablets;

USP 31: Estropipate Tablets; Estropipate Vaginal Cream.

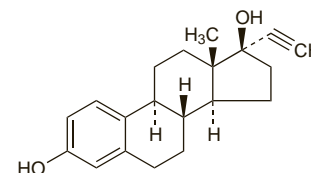
Proprietary Preparations (details are given in Part 3)

Austral.: Genoral; Ogen; **Canad.:** Ogen; **Indon.:** Ogen; **Irl.:** Harmogen; **Mex.:** Ogen; **S.Afr.:** Ortho-Est; **UK:** Harmogen; **USA:** Ogen; Ortho-Est†.

Ethinylestradiol (BAN, rINN)

Aethinylloestradiolum; Ethinyl Estradiol; Ethinylestradiol; Ethinylestradiolum; Ethinylloestradiol; Etinilestradiol; Etinilestradioli; Etinilöstradiol; Etinilösztadiol; Ethinylestradiol; Ethinylestradioli; Etninylestradiol; NSC-10973. 17 α -Ethinylestra-1,3,5(10)-triene-3,17 β -diol; 19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17 β -diol.

ЭТИНИЛЭСТРАДИОЛ
 $C_{20}H_{24}O_2 = 296.4$.
 CAS — 57-63-6.
 ATC — G03CA01; L02AA03.
 ATC Vet — QG03CA01; QL02AA03.



NOTE. Compounded preparations of ethinylestradiol may be represented by the following names:

• Co-cyprindiol (BAN)—ethinylestradiol 35 parts and cyproterone acetate 2000 parts (w/w).

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

Ph. Eur. 6.2 (Ethinylestradiol). A white to slightly yellowish-white, crystalline powder. Practically insoluble in water; freely soluble in alcohol; dissolves in dilute alkaline solutions. Protect from light.

USP 31 (Ethinyl Estradiol). A white to creamy white, odourless, crystalline powder. Insoluble in water; soluble in alcohol, in chloroform, in ether, in vegetable oils, and in solutions of fixed alkali hydroxides. Store in nonmetallic airtight containers. Protect from light.

The symbol † denotes a preparation no longer actively marketed

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). See also under Hormonal Contraceptives, p.2059.

Effects on calcium homeostasis. Two patients with metastatic breast cancer given ethinylestradiol developed rapidly progressive irreversible and fatal hypercalcaemia, considered to be due to stimulation of osteolysis by the oestrogen.¹

1. Cornbleet M, *et al.* Fatal irreversible hypercalcaemia in breast cancer. *BMJ* 1977; **1**: 145.

Effects on the liver. Cholestasis and pruritus developed in a liver transplant recipient receiving ethinylestradiol at a dose of 50 micrograms daily for the treatment of menorrhagia.¹ Symptoms subsided on withdrawal of ethinylestradiol but returned on its re-introduction.

1. Fedorkow DM, *et al.* Cholestasis induced by oestrogen after liver transplantation. *BMJ* 1989; **299**: 1080-1.

Interactions

See under Hormonal Contraceptives, p.2067.

◇ Reviews.

1. Zhang H, *et al.* Pharmacokinetic drug interactions involving 17 α -ethinylestradiol: a new look at an old drug. *Clin Pharmacokinet* 2007; **46**: 133-57.

Pharmacokinetics

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal tract. The presence of an ethinyl group at the 17-position greatly reduces hepatic first-pass metabolism compared with estradiol, enabling the compound to be much more active by mouth, but there is some initial conjugation by the gut wall, and the systemic bioavailability is only about 40%. Ethinylestradiol is highly protein bound, but unlike naturally occurring oestrogens, which are mainly bound to sex-hormone binding globulin, it is principally bound to albumin. It is metabolised in the liver, initially by aromatic hydroxylation catalysed by the cytochrome P450 isoenzyme CYP3A4, to form 2-hydroxyethinylestradiol and various conjugated metabolites. These are excreted in urine and faeces. Metabolites undergo enterohepatic recycling.

◇ References.

1. Back DJ, *et al.* The gut wall metabolism of ethinylestradiol and its contribution to the pre-systemic metabolism of ethinylestradiol in humans. *Br J Clin Pharmacol* 1982; **13**: 325-30.
2. Guengerich FP. Metabolism of 17 α -ethinylestradiol in humans. *Life Sci* 1990; **47**: 1981-8.
3. van den Heuvel MW, *et al.* Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005; **72**: 168-74.

Uses and Administration

Ethinylestradiol is a synthetic oestrogen with actions similar to those of estradiol (see p.2098).

It is frequently used as the oestrogenic component of combined oral contraceptive preparations; a typical daily dose is 20 to 40 micrograms (for guidance on appropriate dose, see p.2069). Ethinylestradiol betadex clathrate has been used similarly in combined oral contraceptives. Ethinylestradiol is also used in a combined contraceptive transdermal patch. A dose of 20 micrograms ethinylestradiol is released daily with norelgestromin. A new patch is applied each week for 3 weeks of a 4-week cycle. Oestrogen exposure from such a patch may be higher than with a comparable oral contraceptive. A combined contraceptive vaginal ring device delivering an average of 15 micrograms ethinylestradiol daily with etonogestrel is also available; it remains in the vagina for 3 weeks and is then removed for a one-week break, after which a new ring is inserted. Ethinylestradiol has also been used orally as an emergency contraceptive (p.2071) combined with levonorgestrel or norgestrel. A combined preparation of ethinylestradiol with the anti-androgen cyproterone is used for the hormonal treatment of acne (p.1577) and hirsutism (p.2089), particularly when contraception is also required (see Uses and Administration, under Cyproterone Acetate, p.2089).

Ethinylestradiol has also been used for **menopausal HRT** (p.2076), although natural oestrogens are usually preferred. Oral doses of 10 to 50 micrograms daily have been given cyclically (with a progestogen in women with a uterus), but preparations providing low-

er doses of 2.5 or 5 micrograms daily are also available.

For the treatment of female **hypogonadism**, doses of 10 to 50 micrograms daily on a cyclical basis have been used.

For the palliative treatment of **prostate cancer** (p.671) doses of 150 micrograms to 3 mg have been given daily. For palliation of malignant neoplasms of the **breast** (p.661) in postmenopausal women doses of 100 micrograms to 1 mg three times daily have been used.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* does include doses of ethinylestradiol. An initial oral dose of 2 micrograms daily may be used in the management of **delayed puberty** (p.2079) in girls. This may be increased every 6 months to 5 micrograms, then to 10 micrograms, then to 20 micrograms daily, according to response. After 12 to 18 months of treatment, a progestogen should be added for 7 days of each 28-day cycle. A daily dose of ethinylestradiol 20 micrograms with cyclical progestogen may then be used to maintain sexual maturation. For the prevention of constitutional **tall stature**, ethinylestradiol may be given to girls aged 2 to 12 years old in a dose of 20 to 50 micrograms daily (see also Growth Disorders in Estradiol, p.2099).

Growth hormone provocation testing may be used in the diagnosis of growth hormone deficiency in children with growth retardation (p.1798). However, the response can be blunted in prepubertal and peripubertal children, resulting in false negative results. Hormonal **pituitary priming** using ethinylestradiol has been tried in both boys and girls in order to increase responsiveness to the test,^{1,2} although there appears to be no consensus on such use.³ The *BNFC* includes an oral dose of 100 micrograms daily for 3 days before the test, for girls with a bone age above 10 years.

1. Loche S, *et al.* The growth hormone response to hexarelin in children: reproducibility and effect of sex steroids. *J Clin Endocrinol Metab* 1997; **82**: 861-4.
2. Coutant R, *et al.* Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. *J Clin Endocrinol Metab* 2001; **86**: 5805-12.
3. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85**: 3990-3. Also available at: <http://www.ghresearchsociety.org/files/Eilat.pdf> (accessed 22/08/08)

Preparations

BP 2008: Ethinylestradiol Tablets; Levonorgestrel and Ethinylestradiol Tablets.

USP 31: Desogestrel and Ethinyl Estradiol Tablets; Ethinyl Estradiol Tablets; Ethinyl Estradiol Tablet and Ethinyl Estradiol Tablets; Levonorgestrel and Ethinyl Estradiol Tablets; Norethindrone Acetate and Ethinyl Estradiol Tablets; Norethindrone and Ethinyl Estradiol Tablets; Norgestimate and Ethinyl Estradiol Tablets; Norgestrel and Ethinyl Estradiol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg: Diva Total; **Austria:** Progynon Cj; **Cz:** Minerva; **Ger:** Progynon Cj; **Hung:** Mikrofolin; **India:** Lynoral; **Indon:** Lynoral; **Israel:** Progynon Cj; **Neth:** Lynoral; **Port:** Jeanine; **Rus:** Microfolin (Микрофоллин); **S.Afr:** Estinyl; **Swed:** Diane; **Switz:** Elleacnelle; **Thai:** Manodoli; **USA:** Estinyl.

Multi-ingredient Arg: Afrodita; Aleli; Anubis; April; Avancel; Bioform; Bioform 35; Cilest; Cuarcic; Cuidafem; Damsel; Diane; Diva; Divina; Dos Dias N; Evelea; Evra; Femexin; Femiane; Ginelea; Ginelea T; Gynovin; Harmonet; Isis; Isis Fe; Kala; Kirumelle; Lindiol; Luviane; Loette; Lutogynestryl; Marvelon; Maxima; Microfilm; Mesconest; Microfilm; Microgynon; Microvar; Milava; Minesse; Minulet; Miranova; Mirelle; Nordette; Nordiol; Norgestrel Minor; Norgestrel Plus; Ovrall; Secret 28; Triestan N; Tridette; Trinordiol; Trinordiol; Venisse; Yasmín; Yasmínelle; **Austral:** Biphasil; Brend-35 ED; Brevinor; Diane; Estelle; Femoden ED; Improvil; Juliette; Levlen ED; Loette; Logynon ED; Marvelon; Microgynon; Microlevlen ED; Minulet; Monofeme; Nordette; Nordiol; Norimin; NuvaRing; NuvaRing ED; Synphasic; Tri-Minulet; Trifeme; Trioden; Triphasil; Triquilar; Valette; Yasmín; **Austria:** Belgyn; Cileste; Dialuna; Diane; Donnina; FemHRT; Femogyn; Gracia; Gynovin; Harmonette; Jeanine; Laurina; Liberal; Loette; Madonella; Marvelon; Meliane; Mercilon; Microgynon; Midane; Minerva; Minesse; Minulet; Mirelle; Mylar; Neo-Stedril; Neogynon; NuvaRing; Ovranelle; Ovsymen; Perikursal; Primosiston; Sequalar; Stedril D; Stengynon; Tri-Minulet; TriClest; Tringynon; Trinordiol; Trinovum; Triodene; Valette; Vivelle; Xylia; Yasmín; Yirala; Yris; **Belg:** Binordiol; Cilest; Claudia; Co-Cyproterone; Cyprodiol; Daphne; Desorelle; Diane; Doccypoeestra; Evra; Femodene; Gestodelle; Gestofeme; Gracia; Gratiella; Harmonet; Lowette; Marvelon; Meliane; Mercilon; Merckelsa; Microgynon; Minestril; Minulet; Mirelle; Neo-Stedril; Neogynon; NuvaRing; Ovidol; Ovsymen; Ratiopharmeva; Stedril 30; Stedril DJ; Tri-Minulet; Tringynon; Trinordiol; Trinovum; Triodene; Yasmín; **Braz:** Adoles; Alexia; Allestra; Anacyclin; Anfert; Artemidis; Ciclo; Cidofemine; Cidion; Cidovulon; Ciprane; Conceptor; Diane; Diminut; Elani; Evnor; Evra; Femiane; Femina; Ferane 35; Fertin; Gestinol; Gestradil; Gestrelan; Ginesse; Gracia; Gynera; Harmonet; Level; Levordiol; Lovelle; Malu; Mercilon; Mercilon Conti; Microdiol; Microfil; Microvar; Minesse; Minin; Minima; Minulet; Mirelle; Neovlar; Nocidin; Nordette; Normamor; Novial; NuvaRing; Ovestra; Previa; Primor; Primosiston; Repopil; Se-lene; Siblima; Tamisa; Tese; Trinordiol; Trinovum; Triquilar; Yasmín; YAZ; **Canada:** Allesse; Brevicon; Cylen; Demulen; Diane; Evra; FemHRT; Loestrin 1.5/30; Marvelon; Min-Ovral; Minestrin; NuvaRing; Ortho 0.5/35; Ortho 1/35; Ortho 7/7/7; Ortho-Cept; Ovrall; Select 1/35; Synphasic; Tri-Cylen; Triphasil; Triquilar; Yasmín; **Chile:** Allesse; Anovulatorio Micro-Dosis; Anuar; Anulette; Belara; Careza; Ciclidon; Ciclomex; Dahlia; Dal; Desorelin; Diane; Dixi-35; Drina; Evilyn; Evra; Farluta; Estrogeno; Femelle; Feminol; Femites; Gracia; Gynera; Gynostat; Harmonet; Innova Cd; Lady-Ten 35; Loette; Lovinda; Mactex; Marvelon; Microfemin; Microgynon; Midalet; Minesse; Miniestrel; Minigest; Minulet; Mirelle; Modutrol; Neofam; Neolette; Nordette; Nordiol; Norvital; NuvaRing; Orion; Primosiston; Tri-Cicloxex; Tri-Mactex; Trifast; Trinordiol; Triquilar; Troit; Yasmín;

Cz: Anteovín; Belanette; Belara; Chloé; Cilest; Diane; Evra; Femoden; Gracia; Gravistat; Harmonet; Jeanine; Jentettin; Katya; Laurina; Lindynette; Loette; Logest; Lunafem; Marvelon; Mercilon; Microgynon; Milligest; Milvanet; Minesse; Minisiston; Minulet; Mirelle; Non-Ovlon; Novynette; NuvaRing; Pramino; Regulon; Restovar; Stedril; Sunya; Tri-Minulet; Tri-Regol; Trinordiol; Trinovum; Triquilar; Trisiston; Vilonet; Vireya; Yadine; Yasmínelle; **Denm:** Cilest; Desorelle; Diane; Dianova; Econ; Evra; Femini; Firionetta; Gestonette; Gracia; Gynatrol; Gynera; Harmonet; Lindynette; Malonetta; Marvelon; Meloden; Mercilon; Microgynon; Milvane; Minulet; Neogestrol; Neogynon; Novynette; NuvaRing; Tetragynon; Tri-Minulet; Triminetta; Trinordiol; Trinovum; Triquilar; Yasmín; **Fin:** Cilest; Cyprest; Diane; Evra; Femoden; Gracia; Harmonet; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Mirelle; Neo-Phimovlar; NuvaRing; Tri-Femoden; Tri-Minulet; Triovlar; Trinordiol; Yasmín; **Fr:** Adepal; Belara; Cilest; Cyclean; Daily; Diane; Effiprev; Evpar; Evra; Harmonet; Holgyeme; Jasmine; Jasminelle; Ludeal; Lumalia; Meliane; Melodia; Mercilon; Minerva; Minesse; Minidril; Miniphase; Minulet; Moneva; NuvaRing; Ortho-Novum 1/35; Phaeva; Planor; Stedril; Tetragynon; Tri-Minulet; Triafem; TriClest; Triella; Trinordiol; Varnoline; **Ger:** Attempta; Balanca; Belara; Bella; Bioli; Cilest; Clevia; Conceplan M; Cyclosa; Cyproderm; Cypronette; Desmin; Diane; Ergalea; Eve; Evra; Femiglo; Femovan; Femranette mikro; Gravistat; Juliette; Lamuna; Leios; Lovell; Lyn-ratiopharm-Sequenz; Marvelon; Microgynon; Minisiston; Minulet; Miranova; MonoStep; Neo-Eunom; Neo-Stedril; Neogynon; Non-Ovlon; Nora-ratiopharm; NovaStep; Novial; NuvaRing; Ostro-Primolut; Ovio; Ovovesta M; Ovsymen; Perikursal; Petibelle; Pramino; Primosiston; Prostinon; Sequalar; Sequostat; Sinovul; Stedril 30; Stedril DJ; Stedril; Synphasic; Tetragynon; Triette; Trigova; Trinordiol; Trinovum; Triquilar; Trisiston; TriStep; Valette; Yasmín; **Gr:** Evra; Gracia; Gynera; Gynofen 35; Harmonette; Laurina; Loette; Marvelon; Meliane; Mercilon; Minulet; Neogynon; Nordette; Nordiol; NuvaRing; Ovrall; Tri-Minulet; Tringyna; Trinordiol; Triquilar; Yasmín; **Hong Kong:** Brevinor; Diane; Eugynon; Evra; Gracia; Gynera; Harmonet; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Neogynon; Nordette; Norimin; Novynette; Rigevidon; Synphase; Tri-Regol; Trinordiol; Trinovum; Triquilar; Yasmín; **Hung:** Anteovín; Belara; Cilest; Cyproxim; Diane; Evra; Femoden; Gracia; Harmonet; Lindynette; Loette; Marvelon; Meliane; Mercilon; Milligest; Minerva; Minesse; Minulet; Miranova; Novynette; NuvaRing; Ovidon; Regulon; Rigevidon; Tri-Minulet; Tri-Regol; Trinordiol; Triodene; Triquilar; Yadine; Yasmínelle; **India:** Diane; Duoluton-L; Femilon; Ginetex; Mixogen; Novelon; Ovilon; Ovipauz-L; Ovrall; Triquilar; **Indon:** Diane; Gynera; Marvelon; Mercilon; Microdiol; Microgynon; Pil Kelurga Berencana; Planak; Trinordiol; Triquilar; Yasmín; **Ir:** Brevinor; Cilest; Diane; Evra; Femodene; Logynon; Marvion; Marvelon; Microgynon 30; Microlet; Minulet; NuvaRing; Ovrall; Ovranelle; Tri-Minulet; Trinordiol; Triodene; Yasmín; **Israel:** Belara; Diane; Estelle; Evra; Feminet; Gynera; Harmonet; Logynon; Meliane; Mercilon; Microdiol; Microgynon; Minesse; Minulet; Neogynon; Nordette; Orchio Cyden; Trinordiol; Yasmín; **Ital:** Arianna; Belara; Diane; Duva; Eogyn; Eugynon; Evnor-DJ; Evra; Fedra; Gionden; Gracia; Harmonet; Loette; Mercilon; Microgynon; Milvane; Minesse; Minulet; Miranova; Novogyn; NuvaRing; Ovranelle; Planum; Pracht; Securin; Tri-Minulet; Tringynon; Trinordiol; Visofol; Yasmín; **Jpn:** Ange; Ortho 7/7/7; **Malaysia:** Diane; Estelle; Gynera; Lindynette; Loette; Marvelon; Meliane; Mercilon; Microgynon 30; Minulet; Nordette; Novynette; Regulon; Rigevidon; Tri-Regol; Trinordiol; Triquilar; Yasmín; **Mex:** Allesse; Belara; Cilest; Diane; Eunice 35-ED; Evra; Femexin; Ginelea; Gynovin; Lettinov; Marvelon; Mercilon; Microgynon; Mileva; Minesse; Minulet; Neogynon; Nordet; Nordiol; Novial; NuvaRing; Ortho-Novum 1/35; Ovrall; Secret 28; Trinordiol; Triquilar; Yasmín; **Neth:** Allesse; Belanette; Cilest; Diane; Evra; Femodene; Gracia; Harmonette; Levent; Logynon; Lovette; Lyndiol; Marvelon; Meliane; Mercilon; Microgynon; Ministat; Minulet; Miranova; Modicon; Neocon; Neogynon; NuvaRing; Ovidol; Ovostat; Rigevidon; Stedril; Tri-Minulet; Tringynon; Trinordiol; Trinovum; Triodene; Yasmín; Yasmínelle; Yira; **Norw:** Diane; Evra; Follimint; Loette; Marvelon; Microgynon; NuvaRing; Synphase; Tetragynon; Trinordiol; Trionetta; Yasmín; **NZ:** Brevinor; Diane; Estelle; Femodene; Leven ED; Loette; Marvelon; Melodene; Mercilon; Microgynon; Minulet; Monofeme; Nordette; Nordiol; Norimin; Ovrall; Synphasic; Trifeme; Trimiron; Triphasil; Triquilar; Yasmín; **Philipp:** Althea; Diane; Evra; Femenal; Gracia; Gynera; Lady; Logynon; Marvelon; Meliane; Mercilon; Microgynon; Microfil; Minulet; Nordette; Nordiol; Rigevidon; Seif; Trinordiol; Trust Pill; Yasmín; **Pol:** Anteovín; Cilest; Cyprest; Diane; Evra; Femoden; Gravistat; Harmonet; Jeanine; Logest; Marvelon; Mercilon; Microgynon; Milvane; Minisiston; Minulet; Mirelle; Novynette; Regulon; Rigevidon; Stedril; Tri-Minulet; Tri-Regol; Trinordiol; Trinovum; Triquilar; Trisiston; Yasmín; Yasmínelle; **Port:** Belara; Diane; Effipen; Estinette; Evra; Femphasoyl; Gracia; Gynera; Harmonet; Laurina; Libel; Marvelon; Mercilon; Microgeste; Microgynon; Minesse; Minigeste; Minulet; Miranova; Neomovon; Novynette; NuvaRing; Petibelle; Regulon; Tetragynon; Tri-Gynera; Tri-Minulet; Trinordiol; Triquilar; Valette; Yasmín; Yasmínelle; **Rus:** Anteovín (Антеовин); Belara (Белара); Cilest (Силест); Diane (Диане); Evra (Евра); Femoden (Фемоден); Jeanine (Жанин); Lindynette (Линдинет); Logest (Логест); Marvelon (Марвелон); Mercilon (Мерсион); Microgynon (Микрогигон); Minisiston (Минисистон); Non-Ovlon (Нон-овлон); Novynette (Новинет); NuvaRing (НоваРинг); Ovidon (Овидон); Regulon (Регулон); Rigevidon (Ригевидон); Tri-Merci (Три-Мерси); Tri-Regol (Три-Регол); Triquilar (Трикуилар); Trisiston (Тризистон); Yarina (Ярина); **S.Afr:** Biphasil; Brevinor; Cilest; Diane; Diva; E-Gen-C; Evra; Femodene ED; Ginetet; Harmonet; Loette; Logynon ED; Marvelon; Melodene; Menoflush; Mercilon; Minerva; Minesse; Minulet; Miranova; Mirelle; Nordette; Nordiol; Ovrall; Tri-Minulet; TriClest; Trinovum; Triodene; Triphasil; Yasmín; **Singapore:** Diane; Estelle; Evra; Gynera; Loette; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Nordette; Trinordiol; Triquilar; Yasmín; **Spain:** Belara; Diane; Evra; Gracia; Gynovin; Harmonet; Loette; Meliane; Melodene 15; Microdiol; Microgynon; Minesse; Minulet; Neogynona; NuvaRing; Ovoplex; Suvarett; Tri-Minulet; Triagynon; Tricidion; Tringynon; Yasmín; Yira; **Swed:** Cilest; Desolett; Evra; Follimint; Follinett; Mercilon; Neovelta; NuvaRing; Orthonett Novum; Restovar; Synphase; Trimiron; Trinordiol; Trinovum; Trionetta; Tringol; Yasmín; **Switz:** Belara; Binordiol; Cilest; Cyprost; Diane; Evra; Femina; Gracia; Gynera; Harmonet; Marvelon; Meloden; Mercilon; Microgynon; Milvane; Minerva; Minesse; Minulet; Miranova; Mirelle; Neogynon; NuvaRing; Ologyn; Ovsymen; Primosiston; Stedril 30; Stedril D; Tetragynon; Tri-Minulet; Trinordiol; Trinovum; Triquilar; Yasmín; **Thai:** Anna; Cilest; Diane; Eugynon 250; Evra; FMP; Gynera; Helen; Hormone Multicapt; Horon; Jery-FMP; Lady-35; Lyndiol; Manoan; Marvelon; Meliane; Mercilon; Microgest; Microgynon; Microlenyn; Minulet; Nordette; Oilezz; Premel; R-Den; Riget; Rigevidon; Sucee; Tri-Clest; Triquilar; Yasmín; **Turk:** Desolett; Diane; Gintera; Lo-Ovral; Microgynon; Minulet; Miranova; Myralon; Preven; Triquilar; Yasmín; **UK:** Accon; Binovum; Brevinor; Cicafem; Cilest; Clairette; Diane; Evra; Eugynon 30; Evra; Femodene; Femodette; Katya; Loestrin; Logynon; Marvelon; Mercilon; Microgynon 30; Minulet; Norimin; Ovrall 30; Ovranelle; Ovsymen; Sunya; Synphase; Tri-Minulet; Triadene; Trinordiol; Trinovum; Yasmín; **USA:** Allesse; April; Aranelle; Aviane; Balziva; Brevicon; Cesia; Crystelle; Cyclessa; Demulen; Denos; Enpresse; Estrostep Fe; Estrostep; Femcon Fe; FemHRT; Jolessa; Junel Fe; Kariva; Kelnor; Leena; Lessina; Levlen; Levlette; Levora; Lo/Ovral; Loestrin; Loestrin Fe; Luterla; Lybrel; Mircette; Modicon; Necon 10/11; Necon 0.5/35; 1/35; NEE 1/35; Nordette; Norinyl 1 + 35; NuvaRing; Ortho Cyden; Ortho Evra; Ortho Tri-Cyden; Ortho-Cept; Ortho-Novum 1/35; Ortho-Novum 10/11; Or-

tho-Novum 7/7/7; Ovcon 35; Ovcon 50; Ovral; Portia; Preven†; Previfem; Quasense; Recipisen; Seasonale; Seasonique; Solia; Sprintec; Sronyx; Tilia Fe; Tri-Legest; Tri-Leven; Tri-Norinyl; Tri-Previfem; Tri-Sprintec; TriNessa; Triphasil; Trivora; Velivet; Yasmin; YAZ; Zentient; Zovia; **Venez.**: Alesse; Belara; Cildidon; Diane; Dixi; Evra; Femiane; Gynera; Harmonet; Marvelon; Mercilon; Minesse; Minigynon; Minulet; Mipil; Mirelle; Neogynon; Nordette; Nordiol; Novial; Ortiler; Ovral; Primoston†; Rigevidon; Tri-Regol; Trinordiol; Triquilar; Yasmin.

Ethylestrenol (BAN, USAN, rINN) ⊗

Éthylestrenol; Ethylestrenolum; Ethiolestrenol; Etilestrenol; Etylestrenol; Etyilestrenoli. 17 α -Ethylestr-4-en-17 β -ol; 19-Nor-17 α -pregn-4-en-17 β -ol.

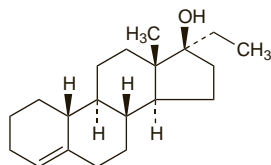
Этилэстренол

$C_{20}H_{32}O = 288.5$.

CAS — 965-90-2.

ATC — A14AB02.

ATC Vet — QA14AB02.



Profile

Ethylestrenol is a 17 α -alkylated anabolic steroid (see Testosterone, p.2129) with little androgenic effect and slight progestogenic activity. It has been used for the promotion of growth in boys with short stature or delayed bone growth. It is used in veterinary medicine.

Etonogestrel (BAN, USAN, rINN)

Etonogestreeli; Étonogestrel; Etonogestrelum; 3-keto-Desogestrel; Org-3236. 13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-3-one; 17 β -Hydroxy-11-methylene-18-homo-19-nor-17 α -pregn-4-en-20-yn-3-one.

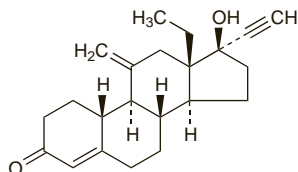
Этоногестрел

$C_{22}H_{28}O_2 = 324.5$.

CAS — 54048-10-1.

ATC — G03AC08.

ATC Vet — QG03AC08.



Adverse Effects and Precautions

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

Breast feeding. Etonogestrel was found in the breast milk of 42 women given a contraceptive etonogestrel implant. Over the 4-month study, compared with a group who used an intra-uterine non-hormonal device, etonogestrel did not affect the volume or composition of breast milk, or the growth of the breast-fed infants.¹ At 3 years of age there was no difference in growth between these 2 groups of children.²

1. Reinprayoon D, *et al.* Effects of the etonogestrel-releasing contraceptive implant (Implanon) on parameters of breastfeeding compared to those of an intrauterine device. *Contraception* 2000; **62**: 239–46.

2. Taneepanichskul S, *et al.* Effects of the etonogestrel-releasing implant Implanon and a nonmedicated intrauterine device on the growth of breast-fed infants. *Contraception* 2006; **73**: 368–71.

Vaginal bleeding. Prolonged vaginal bleeding, lasting from 2 to 26 weeks, has been reported with the use of etonogestrel subdermal implants. Blood transfusion was needed in the management of one patient.¹ Heavy bleeding has been described in 2 women after the implant had broken while in place.^{2,3}

1. Adverse Drug Reactions Advisory Committee (ADRAC). Implanon and vaginal bleeding. *Aust Adverse Drug React Bull* 2003; **22**: 11–12. Also available at: <http://www.tga.gov.au/adr/aadr/aadr0306.pdf> (accessed 27/06/08)

2. Pickard S, Bacon L. Persistent vaginal bleeding in a patient with a broken Implanon. *J Fam Plann Reprod Health Care* 2002; **28**: 207–8.

3. Agrawal A, Robinson C. Spontaneous snapping of an Implanon in two halves in situ. *J Fam Plann Reprod Health Care* 2003; **29**: 238.

Interactions

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

The symbol † denotes a preparation no longer actively marketed

Pharmacokinetics

Etonogestrel is highly bound to plasma proteins; about 32% is bound to sex hormone binding globulin and 66% to albumin. It is metabolised by the cytochrome P450 isoenzyme CYP3A4, and both metabolites and unchanged drug are excreted in the urine and faeces. The elimination half-life is about 25 to 30 hours. Etonogestrel is distributed into breast milk.

⊕ References.

1. Timmer CJ, Mulders TMT. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. *Clin Pharmacokinet* 2000; **39**: 233–42.

2. Bennink HJ. The pharmacokinetics and pharmacodynamics of Implanon, a single-rod etonogestrel contraceptive implant. *Eur J Contracept Reprod Health Care* 2000; **5** (suppl 2): 12–20.

Uses and Administration

Etonogestrel, the active metabolite of desogestrel (p.2093), is used as a hormonal contraceptive (see p.2069). A subdermal implant containing 68 mg of etonogestrel is used as a progestogen-only contraceptive that is effective for 3 years. Etonogestrel is also used as the progestogen component of a combined contraceptive delivered via a vaginal ring device. The ring releases an average of 120 micrograms daily of etonogestrel and 15 micrograms daily of ethinylestradiol and remains in the vagina for 3 weeks; it is then removed for a one-week break after which a new ring is inserted.

Etonogestrel is under investigation as a male contraceptive, given orally or by implant, with testosterone implants or injections.

⊕ References.

1. Edwards JE, Moore A. Implanon: a review of clinical studies. *Br J Fam Plann* 1999; **24**: 3–16.

2. Le J, Tsourounis C. Implanon: a critical review. *Ann Pharmacother* 2001; **35**: 329–36.

3. Roumen F. Contraceptive efficacy and tolerability with a novel combined contraceptive vaginal ring, NuvaRing. *Eur J Contracept Reprod Health Care* 2002; **7** (suppl 2): 19–24.

4. Meirik O, *et al.* WHO Consultation on Implantable Contraceptives for Women. Implantable contraceptives for women. *Hum Reprod Update* 2003; **9**: 49–59.

5. Sarkar NN. The combined contraceptive vaginal device (NuvaRing): a comprehensive review. *Eur J Contracept Reprod Health Care* 2005; **10**: 73–8.

6. Roumen FJ. The contraceptive vaginal ring compared with the combined oral contraceptive pill: a comprehensive review of randomized controlled trials. *Contraception* 2007; **75**: 420–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Implanon†; **Austral.:** Implanon; **Austria:** Implanon; **Belg.:** Implanon; **Braz.:** Implanon; **Chile:** Implanon; **Cz.:** Implanon; **Denm.:** Implanon; **Fin.:** Implanon; **Fr.:** Implanon; **Ger.:** Implanon; **Gr.:** Implanon†; **Hung.:** Implanon; **Indon.:** Implanon; **Irl.:** Implanon; **Ital.:** Implanon†; **Malaysia:** Implanon; **Mex.:** Implanon; **Neth.:** Implanon; **Norw.:** Implanon; **Port.:** Implanon; **Singapore:** Implanon; **Spain:** Implanon; **Swed.:** Implanon; **Switz.:** Implanon; **Thal.:** Implanon; **Turk.:** Implanon; **UK:** Implanon; **USA:** Implanon; **Venez.:** Implanon.

Multi-ingredient: **Austral.:** NuvaRing; **Austria:** NuvaRing; **Belg.:** NuvaRing; **Braz.:** NuvaRing; **Canad.:** NuvaRing; **Chile:** NuvaRing; **Cz.:** NuvaRing; **Denm.:** NuvaRing; **Fin.:** NuvaRing; **Fr.:** NuvaRing; **Ger.:** NuvaRing; **Gr.:** NuvaRing; **Hung.:** NuvaRing; **Irl.:** NuvaRing; **Ital.:** NuvaRing; **Mex.:** NuvaRing; **Neth.:** NuvaRing; **Norw.:** NuvaRing; **Port.:** NuvaRing; **Rus.:** NuvaRing (НоваРинг); **Spain:** NuvaRing; **Swed.:** NuvaRing; **Switz.:** NuvaRing; **USA:** NuvaRing.

Etynodiol Diacetate (BANM, pINN)

Aethynodiolum Diaceticum; Diacetato de etinodiol; Ethynodiol Diacetate (USAN); Étynodiol, Diacetate d'; Etynodioli Diacetat; SC-11800. 19-Nor-17 α -pregn-4-en-20-yn-3 β ,17 β -diol diacetate.

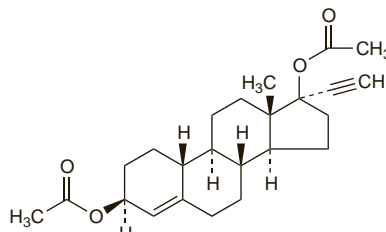
ЭТИНОДИОЛА ДИАЦЕТАТ

$C_{24}H_{32}O_4 = 384.5$.

CAS — 1231-93-2 (etynodiol); 297-76-7 (etynodiol diacetate).

ATC — G03DC06.

ATC Vet — QG03DC06.



Pharmacopoeias. In Br, Pol., and US.

BP 2008 (Etynodiol Diacetate). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform and in ether. Protect from light.

USP 31 (Etynodiol Diacetate). A white, odourless, crystalline powder. Insoluble in water; soluble in alcohol; very soluble in chloroform; freely soluble in ether; sparingly soluble in fixed oils. Protect from light.

Adverse Effects and Precautions

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

Pregnancy. Fetal adrenal cytomegaly in a 17-week-old fetus was associated with the maternal ingestion of an oral contraceptive containing etynodiol diacetate 2 mg and mestranol 100 micrograms from the sixth to the fourteenth week of pregnancy.¹

1. Gau GS, Bennett MJ. Fetal adrenal cytomegaly. *J Clin Pathol* 1979; **32**: 305–6.

Interactions

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

Pharmacokinetics

Etynodiol diacetate is readily absorbed from the gastrointestinal tract and rapidly metabolised, largely to norethisterone (p.2119). About 60% of a dose is stated to be excreted in urine and about 30% in faeces; the half-life in plasma is about 25 hours.

Uses and Administration

Etynodiol diacetate is a progestogen (see Progesterone, p.2126) that is used as the progestogenic component of combined oral contraceptives and also alone as an oral progestogen-only contraceptive (see p.2069); typical daily doses are 1 or 2 mg in combination products and 500 micrograms for progestogen-only contraceptives.

Preparations

USP 31: Ethynodiol Diacetate and Ethinyl Estradiol Tablets; Ethynodiol Diacetate and Mestranol Tablets.

Proprietary Preparations (details are given in Part 3)

Cz.: Femulen†; **Hung.:** Continuit†; **Israel:** Femulen†; **NZ:** Femulen†; **UK:** Femulen.

Multi-ingredient: **Arg.:** Soluna; **Canad.:** Demulen; **USA:** Demulen†; **Kelnor;** Zovia.

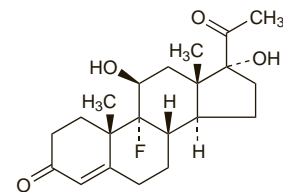
Flugestone Acetate (BANM, rINN)

Acetato de flugestona; Flugestone, Acétate de; Flugestoni Acetas; Flurogestone Acetate (USAN); NSC-65411; SC-9880. 9 α -Fluoro-11 β ,17 α -dihydroxypregn-4-ene-3,20-dione 17-acetate.

Флугестона Ацетат

$C_{23}H_{31}FO_5 = 406.5$.

CAS — 337-03-1 (flugestone); 2529-45-5 (flugestone acetate).



(flugestone)

Profile

Flugestone acetate is a progestogen (see Progesterone, p.2125) used in veterinary medicine.

Fluoxymesterone (BAN, rINN) ⊗

Fluoksimesteroni; Fluoximesteron; Fluoximesterona; Fluoxymestérone; Fluoxymesteronum; Fluximesterona; NSC-12165. 9 α -Fluoro-11 β ,17 β -dihydroxy-17 α -methylandrosta-4-en-3-one.

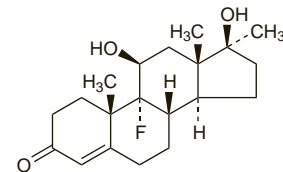
Флуоксиместерон

$C_{20}H_{28}FO_3 = 336.4$.

CAS — 76-43-7.

ATC — G03BA01.

ATC Vet — QG03BA01.



Pharmacopoeias. In Jpn and US.

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

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130).

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)