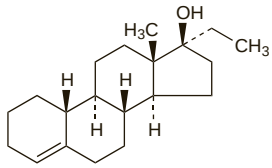
tho-Novum 7/7/7; Ovcon 35; Ovcon 50; Ovral; Portia; Preven†; Previfem; Quasense; Reclipsen; Seasonale; Seasonique; Solia; Sprintec; Sronyx; Tilia Fe; Tri-Legest; Tri-Levlen; Tri-Norinyl; Tri-Previfem; Tri-Sprintec; TriNessa; Triphasil; Trivora; Velivet; Yasmin; YAZ; Zenchent; Zovia; ***Venez.:*** Alesse;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

Ethylestrenol *(BAN, USAN, rINN)* ⊗

Éthylestrénol; Ethylestrenolum; Ethyloestrenol; Etilestrenol; Etylestrenol; Etyyliestrenoli. 17α-Ethylestr-4-en-17β-ol; 19-Nor-17α-pregn-4-en-17β-ol.

Этилэстренол

$C_{20}H_{32}O$ = 288.5.
CAS — 965-90-2.
ATC — A14AB02.
ATC Vet — QA14AB02.



Profile

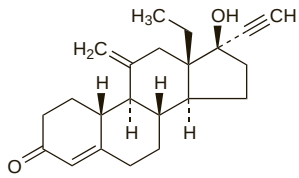
Ethylestrenol is a 17α-alkylated anabolic steroid (see Testosterone, p.2129) with little androgenic effect and slight progestogenic activity. It has been used for the promotion of growth in boys with short stature or delayed bone growth. It is used in veterinary medicine.

Etonogestrel *(BAN, USAN, rINN)*

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

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; ***Thai.:*** Implanon; ***Turk.:*** Implanon; ***UK:*** Implanon; ***USA:*** Implanon; ***Venez.:*** Implanon.

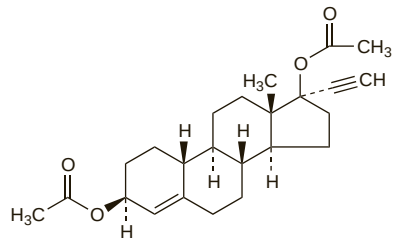
Multi-ingredient: ***Austral.:*** NuvaRing; ***Austria:*** NuvaRing; ***Belg.:*** NuvaRing; ***Braz.:*** NuvaRing; ***Canad.:*** NuvaRing; ***Chile:*** NuvaRing; ***Cz.:*** NuvaRing; ***Denm.:*** NuvaRing; ***Fin.:*** NuvaRing; ***Fr.:*** NuvaRing; ***Ger.:*** NuvaRing; ***Gr.:*** NuvaRing; ***Hung.:*** 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, pINNM)*

Aethynodiolum Diaceticum; Diacetato de etinodiol; Ethynodiol Diacetate *(USAN)*; Étynodiol, Diacetate d'; Etynodioli Diacetas; SC-11800. 19-Nor-17α-pregn-4-en-20-yne-3β,17β-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.:*** Continuin†; ***Israel:*** Femulen†; ***NZ:*** Femulen; ***UK:*** Femulen.

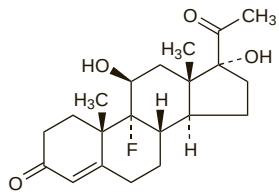
Multi-ingredient: ***Arg.:*** Soluna; ***Canad.:*** Demulen; ***USA:*** Demulen†; Kelnor; Zovia.

Flugestone Acetate *(BANM, rINNM)*

Acetato de flugestona; Flugestone, Acétate de; Flugestoni Acetas; Flurogestone Acetate *(USAN)*; NSC-65411; SC-9880. 9α-Fluoro-11β,17α-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

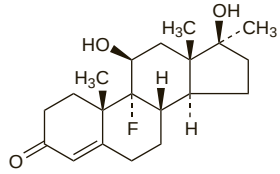
Flugestone acetate is a progestogen (see Progesterone, p.2125) used in veterinary medicine.

Fluoxymesterone *(BAN, rINN)* ⊗

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

Флуоксиместерон

$C_{20}H_{29}FO_3$ = 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).

As with other 17α-alkylated compounds fluoxymesterone may cause hepatotoxicity, and is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Hepatic function should be monitored during therapy.

Uses and Administration

Fluoxymesterone has androgenic properties (see Testosterone, p.2131). It is effective when given orally and is more potent than methyltestosterone.

In the treatment of male hypogonadism (p.2079), fluoxymesterone has been given in a dosage of 5 to 20 mg daily. For the use of fluoxymesterone in boys with delayed puberty, see Administration in Children, below. In the palliation of inoperable neoplasms of the breast in postmenopausal women (p.661) it has been given in daily doses of up to 40 mg. Fluoxymesterone has also been used in the treatment of aplastic anaemia.

Administration in children. In the treatment of delayed puberty (p.2079) in boys fluoxymesterone has been given orally in usual daily doses of 2.5 to 10 mg, adjusted according to response (doses up to 20 mg daily have been used). Care is necessary because of the risk of epiphyseal closure and treatment is generally only given for 4 to 6 months.

Preparations

USP 31: Fluoxymesterone Tablets.

Proprietary Preparations (details are given in Part 3)
Hong Kong: Halotestin†; ***Mex.:*** Stenox; ***Thai.:*** Halotestin†; ***USA:*** Androxy.

Multi-ingredient: ***Arg.:*** Ferona.

Follicle-stimulating Hormone ⊗

Folitropina; FSH.

ATC Vet — QG03GA90.

Follitropin Alfa *(BAN, rINN)* ⊗

Folitropin Alfa; Folitropina alfa; Follitropine Alfa; Follitropinum Alfa.

Фоллитропин Альфа

$C_{437}H_{682}N_{122}O_{134}S_{13}$ = 10 206 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ = 12 485 (β-subunit).

CAS — 9002-68-0 (follitropin alfa); 56832-30-5 (α-subunit); 110909-60-9 (β-subunit); 146479-72-3 (follitropin alfa).

ATC — G03GA05.

ATC Vet — QG03GA05.

Follitropin Beta *(BAN, rINN)* ⊗

Folitropin Beta; Folitropina beta; Follitropine Bêta; Follitropinum Beta; Org-32489.

Фоллитропин Бета

$C_{437}H_{682}N_{122}O_{134}S_{13}$ = 10 206 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ = 12 485 (β-subunit).

CAS — 169108-34-3 (follitropin beta); 150490-84-9 (follitropin beta); 56832-30-5 (α-subunit); 110909-60-9 (β-subunit).

ATC — G03GA06.

ATC Vet — QG03GA06.

Units

80 units of human pituitary follicle-stimulating hormone are contained in about 4.17 micrograms (with 5 mg of mannitol and 1 mg human serum albumin) in one ampoule of the first International Standard (1986).

138 units of recombinant human follicle-stimulating hormone for bioassay are contained in one ampoule of the first International Standard (1995).

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p.2109.

Spongiform encephalopathies. In a few countries, gonadotrophins derived from cadaver pituitary glands have been used in the treatment of infertility, and a small number of patients are reported to have acquired Creutzfeldt-Jakob disease from such preparations.[1] However, most countries have preferred to use gonadotrophins derived from urine,[1] and these in their turn are being replaced with recombinant products;[2] such preparations appear to carry negligible risk of transmitting prion disease.[3-5]

1. Healy DL, Evans J. Creutzfeldt-Jakob disease after pituitary gonadotrophins. *BMJ* 1993; **307:** 517–18.
2. Eshkol A, Page ML. Human gonadotrophin preparations. *BMJ* 1994; **308:** 789.
3. Matorras R, Rodríguez-Escudero FJ. Bye-bye urinary gonadotrophins? The use of urinary gonadotrophins should be discouraged. *Hum Reprod* 2002; **17:** 1675.
4. Balen A. Is there a risk of prion disease after the administration of urinary-derived gonadotrophins? *Hum Reprod* 2002; **17:** 1676–80.
5. Jansen C. Bye-bye urinary gonadotrophins? Reply to debate. *Hum Reprod* 2003; **18:** 895–6.

Pharmacokinetics

Follitropins alfa and beta are slowly absorbed after subcutaneous or intramuscular injection, with an absolute bioavailability of about 70 to 80%. Peak plasma concentrations of follitropin beta have been stated to occur about 12 hours after subcutaneous or intramuscular injection. Accumulation occurs with repeated doses, reaching a steady state within 3 to 5 days. Follitropins are slowly eliminated from the body, with a terminal half-life ranging from 12 to 70 hours. About one-eighth of a dose of follitropin alfa is reported to be excreted in the urine.

◊ References.

1. Karlsson MO, *et al.* The population pharmacokinetics of recombinant- and urinary-human follicle stimulating hormone in women. *Br J Clin Pharmacol* 1998; **45:** 13–20.

Uses and Administration

Follicle-stimulating hormone is secreted by the anterior lobe of the pituitary gland, with another gonadotrophin, luteinising hormone (p.2112).

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova; in men it has a role in spermatogenesis.

Recombinant human follicle-stimulating hormones (follitropins alfa or beta) are used in the treatment of female infertility due to anovulation, in women who have not responded to clomifene therapy. Follitropins are also used for the stimulation of spermatogenesis in the management of male infertility caused by hypogonadotrophic hypogonadism (see Infertility, p.2080).

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. In menstruating patients treatment should be started within the first 7 days of the menstrual cycle.

- Treatment is usually begun with 75 to 150 units daily by subcutaneous or intramuscular injection for 7 or 14 days; if there is no response, dosage is increased at 7- or 14-day intervals until an adequate but not excessive response is achieved.
- Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation.

It has been suggested in UK licensed product information for follitropin alfa that a daily dose of 225 units is the usual maximum, and that if a patient fails to respond adequately after 4 weeks of treatment that cycle should be abandoned and the patient should subsequently begin the next cycle at a higher starting dose.

Follitropins are also used as part of IVF or other assisted reproductive technologies.

- For this purpose doses of 150 to 225 units daily are generally given, for at least 4 days, commencing on the second or third day of the menstrual cycle. Thereafter the dose may be adjusted individually based on ovarian response to a usual maximum of about 450 units; adequate follicular development generally occurs within about 5 to 10 days of treatment.
- Pituitary downregulation with a gonadorelin analogue may be used with follitropin therapy, in which case the gonadorelin analogue is generally begun about 2 weeks before follitropin, and the 2 are then continued together until follicular development is adequate.
- A single dose of up to 10 000 units of chorionic gonadotrophin is then given to induce final follicular maturation and oocyte retrieval performed about 35 hours later.

Follitropins are used for the stimulation of spermatogenesis in the management of **male infertility** caused by hypogonadotrophic hypogonadism. Before starting follitropin therapy, chorionic gonadotrophin is given to raise serum testosterone concentrations to the normal range, which may take 3 to 6 months. A dose of follitropin alfa or beta of 150 units subcutaneously three times weekly is then used, with continued chorionic gonadotrophin; doses of follitropin alfa up to 300 units three times weekly may be required. Treatment is continued for at least 4 months, and more than 18 months of treatment may be needed. A dose of follitropin beta 75 units daily or two or three times weekly, by subcutaneous or intramuscular injection, has been used similarly.

Other substances with follicle-stimulating activity are used similarly: these include human menopausal gonadotrophins (p.2109), which have both luteinising and follicle-stimulating activity, and urofollitropin (p.2136).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gonal-F; Puregon; ***Austral.:*** Gonal-F; Puregon; ***Austria:*** Gonal-F; Puregon; ***Belg.:*** Gonal-F; Puregon; ***Braz.:*** Gonal-F; Puregon; ***Canad.:*** Gonal-F; Puregon; ***Chile:*** Gonal-F†; Puregon; ***Cz.:*** Gonal-F; Puregon; ***Denm.:*** Gonal-F; Puregon; ***Fin.:*** Gonal-F; Puregon; ***Fr.:*** Gonal-F; Puregon; ***Ger.:*** Gonal-F; Puregon; ***Gr.:*** Gonal-F; Puregon; ***Hong Kong:*** Gonal-F; Puregon; ***Hung.:*** Gonal-F; Puregon; ***India:*** Gonal-F; ***Indon.:*** Gonal-F; Puregon; ***Irl.:*** Gonal-F; Puregon; ***Israel:*** Gonal-F; Puregon; ***Ital.:*** Gonal-F; Puregon; ***Malaysia:*** Gonal-F; Puregon; ***Mex.:*** Gonal-F; Puregon; ***Neth.:*** Gonal-F; Puregon; ***Norw.:*** Gonal-F; Puregon; ***NZ:*** Gonal-F; Puregon; ***Philipp.:*** Gonal-F; Puregon; ***Pol.:*** Gonal-F; Puregon; ***Port.:*** Gonal-F; Puregon; ***Rus.:*** Gonal-F (Гонал-Ф); Puregon (Пуреон); ***S.Afr.:*** Gonal-F; Puregon†; ***Singapore:*** Gonal-F; Puregon; ***Spain:*** Gonal-F; Puregon; ***Swed.:*** Gonal-F; Puregon; ***Switz.:*** Gonal-F; Puregon; ***Thai.:*** Gonal-F; Puregon; ***Turk.:*** Gonal-F; Puregon; ***UK:*** Gonal-F; Puregon; ***USA:*** Follistim; Gonal-F; ***Venez.:*** Gonal-F; Puregon.

Multi-ingredient: ***Cz.:*** Pergoveris; ***Port.:*** Pergoveris; ***UK:*** Pergoveris.

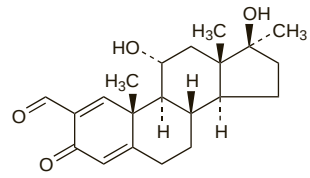
Formebolone *(BAN, rINN)* ⊗

Formebolona; Formébolone; Formebolonum; Formyldienolone. 11α,17β-Dihydroxy-17β-methyl-3-oxoandrosta-1,4-diene-2-carbaldehyde.

Формеболон

$C_{21}H_{28}O_4$ = 344.4.

CAS — 2454-11-7.



Profile

Formebolone has been used for its anabolic properties (see Testosterone, p.2129). It appears to be widely abused by body-builders.

Fosfestrol *(BAN, rINN)*

Diethylstilbestrol Diphosphate; Fosfestroli; Fosfestrolum; Phosphoestrolum; Stilboestrol Diphosphate. (*E*)-α,α′-Diethylstilbene-4,4′-diol bis(dihydrogen phosphate); (*E*)-4,4′-(1,2-Diethylvinylene)bis(phenyl dihydrogen orthophosphate).

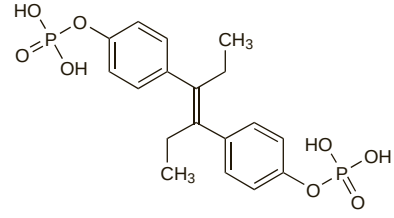
Фосфэстрол

$C_{18}H_{22}O_8P_2$ = 428.3.

CAS — 522-40-7.

ATC — L02AA04.

ATC Vet — QL02AA04.



Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Diethylstilbestrol Diphosphate). An off-white, odourless, crystalline powder. Sparingly soluble in water; soluble in alcohol and in dilute alkali. Store in airtight containers at a temperature not exceeding 21°.