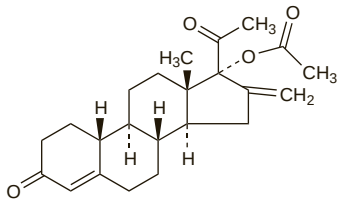
Elcometrine

Elcometrina; 16-Methylene-17-alpha-acetoxy-19 Norprogesterone; ST-1435.

$C_{23}H_{30}O_4$ = 370.5.
CAS — 7759-35-5.



Profile

Elcometrine is a synthetic progestogen that is being developed for use in contraception and menopausal HRT, and in the management of endometriosis.

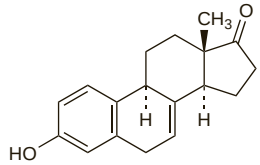
◊ References.

1. Ylänen K, *et al.* Subdermal progestin implant (Nestorone) in the treatment of endometriosis: clinical response to various doses. *Acta Obstet Gynecol Scand* 2003; **82:** 167–72.
2. Sitruk-Ware R, *et al.* Nestorone : clinical applications for contraception and HRT. *Steroids* 2003; **68:** 907–13.
3. Sivin I, *et al.* Two-year performance of a Nestorone -releasing contraceptive implant: a three-center study of 300 women. *Contraception* 2004; **69:** 137–44.
4. Sivin I, *et al.* Contraceptive vaginal rings releasing Nestorone and ethinylestradiol: a 1-year dose-finding trial. *Contraception* 2005; **71:** 122–9.
5. Fraser IS, *et al.* Serum Nestorone and ethinyl estradiol levels, and ovulation inhibition in women using three different dosage combinations of a Nestorone progestogen-ethinyl estradiol contraceptive vaginal ring on a bleeding-signaled regimen. *Contraception* 2005; **72:** 40–5.
6. Weisberg E, *et al.* Clinical performance and menstrual bleeding patterns with three dosage combinations of a Nestorone progestogen/ethinyl estradiol contraceptive vaginal ring used on a bleeding-signaled regimen. *Contraception* 2005; **72:** 46–52.
7. Croxatto HB, *et al.* Feasibility study of Nestorone -ethinylestradiol vaginal contraceptive ring for emergency contraception. *Contraception* 2006; **73:** 46–52.

Equilin

Equilina. 3-Hydroxyestra-1,3,5(10),7-tetraen-17-one.

$C_{18}H_{20}O_2$ = 268.4.
CAS — 474-86-2.



Pharmacopoeias. In *US.*
USP 31 (Equilin). Store in airtight containers. Protect from light.

Profile

Equilin is a natural oestrogenic hormone found in horses. Sodium equilin sulfate is one of the components of both conjugated oestrogens (p.2087) and esterified oestrogens (see below) used for menopausal HRT.

Esterified Oestrogens

Esterified Estrogens; Estrógenos esterificados.

Эстрогены Этерифицированные

Pharmacopoeias. In *US.*
USP 31 (Esterified Estrogens). A mixture of the sodium salts of the sulfate esters of the oestrogenic substances, principally estrone. It contains 75 to 85% of sodium estrone sulfate and 6 to 15% of sodium equilin sulfate, in such a proportion that the total of these two components is not less than 90%, of the labelled amount of esterified oestrogens. A white or buff-coloured amorphous powder; odourless or having a slight characteristic odour. Store in airtight containers.

Profile

Esterified oestrogens have actions and uses similar to those described for estradiol (see below). They are used for the same purposes (principally menopausal HRT), and in a similar oral dosage, as conjugated oestrogens (see p.2087), although higher cyclical doses of 2.5 to 7.5 mg daily are still licensed for use in female hypogonadism.

Preparations

USP 31: Esterified Estrogens Tablets.

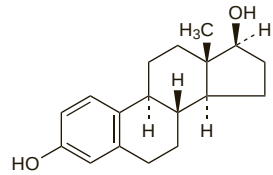
Proprietary Preparations (details are given in Part 3)
Arg.: Menest†; ***Chile:*** Femibel; ***Switz.:*** Oestro-Feminal†; ***USA:*** Estratab; Menest.

Multi-ingredient: ***Chile:*** Delitan; Feminova-T; ***USA:*** Covaryx; Estratest; Syntest.

Estradiol *(BAN, rINN)*

Beta-oestradiol; Dihidrofoliculina; Dihidroxiestratrieno; Dihidroxiestrina; Dihydrofolliculin; Dihydrotheelin; Dihydroxyoestrin; Estradioli; Estradiolis; Estradiolum; NSC-9895; Oestradiol; Östradiol; Ösztradiol. Estra-1,3,5(10)-triene-3,17β-diol.

Эстрадиол
$C_{18}H_{24}O_2$ = 272.4.
CAS — 50-28-2 (anhydrous estradiol).
ATC — G03CA03.
ATC Vet — QG03CA03.



NOTE. In *Martindale* the term oestradiol is used for the endogenous substance.

Pharmacopoeias. In *Chin.* and *US.*
Eur. (see p.vii) includes the hemihydrate.
Ph. Eur. 6.2 (Estradiol Hemihydrate). A white or almost white crystalline powder or colourless crystals. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; slightly soluble in dichloromethane.
USP 31 (Estradiol). White or creamy-white, odourless, hygroscopic small crystals or crystalline powder. Practically insoluble in water; soluble 1 in 28 of alcohol, 1 in 435 of chloroform, and 1 in 150 of ether; soluble in acetone, in dioxan, and in solutions of fixed alkali hydroxides; sparingly soluble in vegetable oils. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Estradiol Acetate *(BANM, USAN, rINNM)*

Acetato de estradiol; E-3A; Estradiol, Acétate d'; Estradiol-3-acetate; Estradioli Acetas; Oestradiol Acetate. Estra-1,3,5(10)-triene-3,17β-diol 3-acetate.

Эстрадиола Ацетат
$C_{20}H_{26}O_3$ = 314.4.
CAS — 4245-41-4.
ATC — G03CA03.
ATC Vet — QG03CA03.

Estradiol Benzoate *(BANM, rINN)*

Benzoato de estradiol; Beta-oestradiol Benzoate; Dihydroxyoestrin Monobenzoate; Estradiol, benzoate d'; Estradiolbensoat; Estradiol-benzoát; Estradioli benzoas; Estradiolibentsoaatti; Estradiolio benzoatas; Estradiolu benzoesan; NSC-9566; Oestradiol Benzoate; Östradiol Benzoat; Ösztradiol-benzoát. Estra-1,3,5(10)-triene-3,17β-diol 3-benzoate.

Эстрадиола Бензоат
$C_{25}H_{28}O_3$ = 376.5.
CAS — 50-50-0.
ATC — G03CA03.
ATC Vet — QG03CA03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Estradiol Benzoate). An almost white crystalline powder or colourless crystals. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in acetone; freely soluble in dichloromethane; slightly soluble in methyl alcohol.
USP 31 (Estradiol Benzoate). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in acetone; slightly soluble in ether. Store in airtight containers. Protect from light.

Estradiol Cipionate *(BANM, rINNM)*

Cipionato de estradiol; Estradiol, Cipionate d'; Estradiol Cypionate; Estradioli Cipionas; Oestradiol Cyclopentylpropionate; Oestradiol Cypionate. Estra-1,3,5(10)-triene-3,17β-diol 17-(3-cyclopentylpropionate).

Эстрадиола Ципионат
$C_{26}H_{36}O_3$ = 396.6.
CAS — 313-06-4.
ATC — G03CA03.
ATC Vet — QG03CA03.

Pharmacopoeias. In *US.*
USP 31 (Estradiol Cypionate). A white to practically white crystalline powder, odourless or has a slight odour. Insoluble in water; soluble 1 in 40 of alcohol, 1 in 7 of chloroform, and 1 in 2800 of ether; soluble in acetone and in dioxan; sparingly soluble in vegetable oils. Store in airtight containers. Protect from light.

Estradiol Dipropionate *(BANM, rINNM)*

Dihydroxyoestrin Dipropionate; Dipropionato de estradiol; Estradiol, Dipropionate d'; Estradioli Dipropionas; Oestradiol Dipropionate. Estra-1,3,5(10)-triene-3,17β-diol dipropionate.

Эстрадиола Дипропионат
$C_{24}H_{32}O_4$ = 384.5.
CAS — 113-38-2.
ATC — G03CA03.
ATC Vet — QG03CA03.

Estradiol Enantate *(BANM, rINNM)*

Enantato de estradiol; Estradiol, Enantate d'; Estradiol Enanthate *(USAN)*; Estradioli Enantas; Oestradiol Enanthate; Oestradiol 17-Heptanoate; SQ-16150. Estra-1,3,5(10)-triene-3,17β-diol 17-heptanoate.

Эстрадиола Энантат
$C_{25}H_{36}O_3$ = 384.6.
CAS — 4956-37-0.
ATC — G03CA03.
ATC Vet — QG03CA03.

Estradiol Hexahydrobenzoate *(BANM, rINNM)*

Estradiol, Hexahydrobenzoate d'; Estradioli Hexahydrobenzoas; Hexahidrobenzoato de estradiol; Oestradiol Hexahydrobenzoate. Estra-1,3,5(10)-triene-3,17β-diol 17-cyclohexanecarboxylate.

Эстрадиола Гексагидробензоат
$C_{25}H_{34}O_3$ = 382.5.
CAS — 15140-27-9.
ATC — G03CA03.
ATC Vet — QG03CA03.

Estradiol Phenylpropionate *(BANM, rINNM)*

Estradiol, Phénylpropionate de; Estradioli Phenylpropionas; Fenilpropionato de estradiol; Oestradiol Phenylpropionate; Östradiol Fenilpropiyonat. Estra-1,3,5(10)-triene-3,17β-diol 17-(3-phenylpropionate).

Эстрадиола Фенилпропионат
$C_{27}H_{32}O_3$ = 404.5.
ATC — G03CA03.
ATC Vet — QG03CA03.

Estradiol Valerate *(BANM, rINN)*

Estradiol, valérate d'; Estradioli valeras; Estradiolio valeratas; Estradiolivaleraatti; Estradiolvalerat; Estradiol-valerát; NSC-17590; Oestradiol Valerate; Östradiol-17-Valerat; Ösztradiol-valerát; Valerato de estradiol. Estra-1,3,5(10)-triene-3,17β-diol 17-valerate.

Эстрадиола Валерат
$C_{23}H_{32}O_3$ = 356.5.
CAS — 979-32-8.
ATC — G03CA03.
ATC Vet — QG03CA03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Estradiol Valerate). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; soluble in alcohol. Protect from light.
USP 31 (Estradiol Valerate). A white crystalline powder which is usually odourless or may have a faint fatty odour. Practically insoluble in water; soluble in benzyl benzoate, in dioxan, in methyl alcohol, and in castor oil; sparingly soluble in arachis oil and in sesame oil. Store in airtight containers. Protect from light.

Adverse Effects

The adverse effects of estradiol and other oestrogens are related, in part, to dose and duration of therapy, and to the gender and age of the recipient. In addition, adverse effects may be modified by a progestogen in combined oral contraceptives or menopausal HRT. Whether adverse effects of natural and synthetic oestrogens differ, and whether the dosage route has an effect, is less clear.

The adverse effects of oestrogens used in hormonal contraceptives are considered in detail starting on p.2059. Those of oestrogens used in HRT are considered in detail starting on p.2071.

The use of oestrogens in children may cause premature closure of the epiphyses resulting in decreased final adult height.

Large doses of oestrogens used in palliation of cancers have also been associated with nausea, fluid retention, venous and arterial thrombosis, and cholestatic jaundice. In men, they cause impotence and feminising effects such as gynaecomastia. In women, they may cause withdrawal bleeding, and, when used for breast cancer, they have caused hypercalcaemia and bone pain.

Effects on the skin. Transdermal patches in which estradiol is dissolved in the adhesive matrix may cause fewer skin reactions than those releasing estradiol from an alcoholic reservoir.

1. Ross D. Randomised crossover comparison of skin irritation with two transdermal oestradiol patches. *BMJ* 1997; **315:** 288.

Precautions

The precautions for the use of estradiol and other oestrogens used as menopausal HRT are considered in detail starting on p.2075. Those for oestrogens used in hormonal contraceptives are considered in detail starting on p.2065.

High doses of oestrogen used in treating malignant disease should be used cautiously in patients with cerebrovascular disorders, coronary artery disease, or venous thromboembolism. They may exacerbate hypercalcaemia of malignancy.

Oestrogens should be used with caution in children because premature closure of the epiphyses may occur resulting in inhibited linear growth and small stature.

Oestrogens have been reported to interfere with some diagnostic tests such as those for thyroid function and glucose tolerance.

Breast feeding. Estradiol has been detected in breast milk after the use of pessaries containing 50 or 100 mg of estradiol.[1] The American Academy of Pediatrics considers that estradiol is usually compatible with breast feeding.[2]

1. Nilsson S, *et al.* Transfer of estradiol to human milk. *Am J Obstet Gynecol* 1978; **132:** 653–7.
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)

Cosmetic use. Use of cosmetic products containing oestrogens has led to adverse effects such as precocious puberty in children[1,2] and gynaecomastia or postmenopausal bleeding in adults.[1] Such products have been used by a greater proportion of African Americans than any other ethnic group in the USA, and it has been hypothesised that this may have contributed to the observations of earlier onset of puberty in girls[3,4] and increased risk of breast cancer in young women.[4]

1. Anonymous. Estrogens in cosmetics. *Med Lett Drugs Ther* 1985; **27:** 54–5.
2. Tiwary CM. Premature sexual development in children following the use of estrogen- or placenta-containing hair products. *Clin Pediatr (Phila)* 1998; **37:** 733–9.
3. Li S-T, *et al.* Hormone-containing hair product use in prepubertal children. *Arch Pediatr Adolesc Med* 2002; **156:** 85–6.
4. Donovan M, *et al.* Personal care products that contain estrogens or xenoestrogens may increase breast cancer risk. *Med Hypotheses* 2007; **68:** 756–66.

Porphyria. Oestrogens are considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Pregnancy. Although gross abnormalities of the genito-urinary tract have been reported in the male offspring of women who took diethylstilbestrol during pregnancy there is conflicting evidence as to whether the oestrogen produced an increased risk of abnormalities, infertility, or testicular cancer in such offspring (see p.2095). The male fetus is normally protected from the feminising effects of the natural oestrogens in the uterine environment by the early development of the testes and the secretion of male hormones.[1] However, there has been considerable concern about a rising incidence of disorders of the male reproductive tract, and a reduction in sperm counts, which has been noted in the last 20 to 30 years. It has been hypothesised that overexposure of male fetuses to environmental oestrogens derived from pollutants such as pesticides and plastics may be responsible for this decline,[2,3] although some dispute this.[4] A systematic review[5] of epidemiological data found no strong evidence to link fetal exposure to oestrogens (as pharmaceuticals or pollutants) with reduced sperm count, cryptorchidism, or hypospadias, although there was some evidence to support a possible link with testicular cancer.

For discussion of the lack of effects of hormonal contraceptives on the fetus, including evidence that they are unlikely to increase the risk of hypospadia in the male fetus, see Pregnancy, under Precautions of Hormonal Contraceptives, p.2067.

1. Mittwoch U, *et al.* Male sexual development in "a sea of oestrogen". *Lancet* 1993; **342:** 123–4.
2. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993; **341:** 1392–5.
3. de Kretser DM. Declining sperm counts. *BMJ* 1996; **312:** 457–8.
4. Thomas JA. Falling sperm counts. *Lancet* 1995; **346:** 635.
5. Storgaard L, *et al.* Male reproductive disorders in humans and prenatal indicators of estrogen exposure: a review of published epidemiological studies. *Reprod Toxicol* 2006; **21:** 4–15.

Veterinary use. An FAO/WHO expert committee examining the risks from residues of veterinary drugs in foodstuffs established an acceptable daily intake for estradiol, but concluded that there would be no need to specify a numerical maximum residue limit for estradiol in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that in the EU the use of steroidal hormones such as oestrogens in veterinary practice is restricted, and their use as growth promotors is banned.

There is concern about the effect of environmental oestrogens on male fertility and development, see Pregnancy, above.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 27/06/08)

Interactions

Interactions involving estradiol and other oestrogens used in menopausal HRT are covered on p.2076. Interactions for oestrogens used in hormonal contraceptives are covered on p.2067.

Pharmacokinetics

In general, estradiol and other oestrogens are readily absorbed from the gastrointestinal tract and through the skin or mucous membranes. However, the natural unconjugated oestrogens such as estradiol undergo extensive first-pass metabolism in the gastrointestinal tract and liver after oral doses. They are, therefore, generally not orally active, although a micronised preparation of estradiol has sufficient bioavailability (3 to 5%) to be orally active. Estradiol is metabolised in part to less active oestrogens such as estriol and estrone. Synthetic oestrogens produced by alkylation of the C17 position, such as ethinylestradiol, are more slowly metabolised and are therefore orally active. Conjugated oestrogens, which are essentially oestrogen metabolites, are also orally active because they are hydrolysed by enzymes in the lower gastrointestinal tract allowing absorption of the active oestrogen. Vaginal, transdermal, intranasal, or parenteral use of oestrogens also avoids first-pass hepatic metabolism. Plasma-estradiol concentrations are reported to reach a peak 1.5 to 2 hours after an oral dose, and again at about 8 hours due to enterohepatic recycling. Estradiol esters are rapidly hydrolysed to free estradiol when given orally. After intramuscular injection of the esters, absorption is prolonged.

Oestrogens are extensively bound to plasma proteins. Naturally occurring oestrogens such as estradiol are principally bound to sex-hormone binding globulin. Conversely, ethinylestradiol is mostly bound to albumin.

Oestrogens are metabolised in the liver. A variety of sulfate and glucuronide conjugates are formed, and these are excreted in the urine and the bile. Those excreted in the bile undergo enterohepatic recycling or are excreted in the faeces.

◊ References to the pharmacokinetics of estradiol[1-4] and other oestrogens.[5,6]

1. Kuhnz W, *et al.* Pharmacokinetics of estradiol, free and total estrone, in young women following single intravenous and oral administration of 17β-estradiol. *Arzneimittelforschung* 1993; **43:** 966–73.
2. Schubert W, *et al.* Pharmacokinetic evaluation of oral 17β-oestradiol and two different fat soluble analogues in ovariectomized women. *Eur J Clin Pharmacol* 1993; **44:** 563–8.
3. Baker VL. Alternatives to oral estrogen replacement: transdermal patches, percutaneous gels, vaginal creams and rings, implants, other methods of delivery. *Obstet Gynecol Clin North Am* 1994; **21:** 271–9.
4. Price TM, *et al.* Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17β-estradiol. *Obstet Gynecol* 1997; **89:** 340–5.
5. Stumpf PG. Pharmacokinetics of estrogen. *Obstet Gynecol* 1990; **75** (suppl): 9S–14S.
6. O'Connell MB. Pharmacokinetic and pharmacologic variation between different estrogen products. *J Clin Pharmacol* 1995; **35** (suppl): 18S–24S.

Uses and Administration

Estradiol is the most active of the naturally occurring oestrogens (for further details, see p.2058). Estradiol and its semisynthetic esters and other natural oestrogens are primarily used as menopausal HRT (see p.2076) whereas synthetic derivatives such as ethinylestradiol and mestranol have a major role as components of combined oral contraceptives (see Hormonal Contraceptives, p.2069). Estradiol may also be used as replacement therapy for female hypogonadism or primary ovarian failure (p.2079). Replacement therapy ('add-back' therapy) may also be given to women in whom the pituitary-ovarian axis is suppressed by therapy with gonadorelin or its analogues.

Estradiol hemihydrate 1.03 mg is equivalent to about 1 mg of the anhydrous substance.

For **menopausal HRT** oral preparations or transdermal patches of estradiol are commonly used. Other transdermal formulations, subcutaneous implants, and a nasal spray are also available. Intramuscular injections were formerly used. In women with a uterus, a progestogen is also required, given cyclically or continuously, usually by mouth although some combined transdermal preparations are available. Local vaginal estradiol preparations are used specifically for the treatment of menopausal atrophic vaginitis; these are generally recommended for short-term use only, if given without a progestogen in women with a uterus, although specific recommendations vary between products.

For use *by mouth* estradiol or estradiol valerate are normally given; doses are 1 or 2 mg daily cyclically or more often continuously. Estradiol acetate may be given in an initial dose of 450 micrograms daily, increasing if necessary to 0.9 or 1.8 mg once daily.

Estradiol may be used topically as *transdermal skin patches* to provide a systemic effect; a variety of patches are available which release between 25 and 100 micrograms of estradiol every 24 hours. A low-dose patch supplying 14 micrograms daily is also available specifically for the prevention of postmenopausal osteoporosis in women at significant risk; with this low dose, the addition of a 14-day course of progestogen in women with a uterus is only required once every 6 to 12 months. Depending on the preparation, patches are replaced once or twice weekly. Each new patch is applied to a different area of skin in rotation, usually below the waistline; patches should not be applied on or near the breasts. *Topical gel* preparations are also used for systemic effect. The usual applied dose is 0.25 to 1.5 mg of estradiol daily, depending on the preparation, but up to 3 mg daily may be required for control of menopausal symptoms in some women. The gel should not be applied on the face or on or near the breasts, vagina, or vulval region. A *topical emulsion* is also available; estradiol hemihydrate 8.7 mg is applied daily to provide a systemic estradiol dose of about 50 micrograms. A *transdermal spray* has also been developed, delivering a single dose of estradiol 1.53 mg onto the skin. It should be applied to the skin of the inner surface of the forearm, and the dose may be increased up to 3 sprays once daily in the morning, at separate sites on the forearm, according to response.

A *nasal spray* is available, delivering 150 micrograms of estradiol hemihydrate per spray. The usual initial dose is 150 micrograms daily (1 spray in 1 nostril). After 2 or 3 cycles the dose may be adjusted according to response; the usual maintenance dose is 300 micrograms daily (1 spray in each nostril once daily) but may range from 150 micrograms once daily up to 450 to 600 micrograms daily in 2 divided doses.

In order to prolong the duration of action *subcutaneous implants* of estradiol may be used. The dose of estradiol is generally 25 to 100 mg with a new implant being given after about 4 to 8 months according to oestrogen concentrations.

Estradiol may be used locally either as 25-microgram *vaginal tablets*, at an initial dose of one tablet daily for 2 weeks followed by a maintenance dose of one tablet twice a week, or as a 0.01% *vaginal cream*, in initial amounts of 2 to 4 g of cream daily for 1 to 2 weeks followed by half the initial dose for a similar period, then a maintenance dose of 1 g up to 3 times weekly. A local delivery system using a 3-month *vaginal ring* contains 2 mg of estradiol hemihydrate, and delivers about 7.5 micrograms of estradiol per 24 hours. Another 3-month vaginal ring system, which contains estradiol acetate, releases either 50 or 100 micrograms of estradiol daily, and is used for the relief of both local and systemic postmenopausal symptoms.

Intramuscular injections of estradiol benzoate or valerate esters have been used as oily depot solutions, usually given once every 3 to 4 weeks. The cipionate, dipropionate, enantate, hexahydrobenzoate, phenylpropionate, and undecylate esters have been used similarly. The enantate and cipionate esters are used as the oestrogen component of combined injectable **contraceptives**.

Estradiol and other oestrogens have sometimes been used in higher doses for palliative treatment in **prostate cancer** (p.671) and **breast cancer** in men and postmenopausal women (p.661).

Administration. ***BUCCAL AND SUBLINGUAL ADMINISTRATION.*** Estradiol is absorbed through the *buccal* route, and has been reported to improve postmenopausal vasomotor symptoms.[1] A pharmacokinetic study[2] of micronised estradiol found the *sublingual* route resulted in more rapid absorption, a higher peak concentration, and more rapid elimination, than oral dosage. Sublingual micronised estradiol has been studied for the management of postpartum depression.[3]

1. Gass MS, *et al.* A short study in the treatment of hot flashes with buccal administration of 17-β estradiol. *Maturitas* 2004; **49:** 140–7.
2. Price TM, *et al.* Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 β-estradiol. *Obstet Gynecol* 1997; **89:** 340–5.
3. Ahokas A, *et al.* Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17β-estradiol: a preliminary study. *J Clin Psychiatry* 2001; **62:** 332–6.

IMPLANTS. There may be a striking interpatient variation in blood-estradiol concentrations in women receiving estradiol implants,[1] and symptoms of oestrogen deficiency have re-appeared in some patients even though serum-estradiol concentrations were within or above the physiological range.[2] After debate on the appropriateness of using serum concentrations of estradiol as a guide to implant use, rather than symptoms,[3-7] it is now recommended that estradiol concentration should be monitored during therapy.

Cyclical progestogen may be required for a prolonged period after removal of estradiol implants in women with a uterus.[7]

1. Guirgis RR. Oestradiol implants: what dose, how often? *Lancet* 1987; **ii:** 856.
2. Gangar K, *et al.* Symptoms of oestrogen deficiency associated with supraphysiological plasma oestradiol concentrations in women with oestradiol implants. *BMJ* 1989; **299:** 601–2.
3. Ginsburg J, Hardiman P. Oestrogen deficiency and oestradiol implants. *BMJ* 1989; **299:** 1031.
4. Studd J, *et al.* Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 1400–1.
5. Swyer GIM. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 854.
6. Tobias JH, Chambers TJ. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 854.
7. Wardle P, Fox R. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 1102.

INTRANASAL ADMINISTRATION. The intranasal route for estradiol HRT has been reviewed.[1] It appears to be comparable in efficacy to oral[2] or transdermal use[3,4] in the treatment of menopausal symptoms. As with transdermal application, the intranasal route avoids intestinal and hepatic first-pass metabolism.

1. Dooley M, *et al.* Estradiol-intranasal: a review of its use in the management of menopause. *Drugs* 2001; **61:** 2243–62.
2. Studd J, *et al.* Efficacy and acceptability of intranasal 17β-oestradiol for menopausal symptoms: randomised dose-response study. *Lancet* 1999; **353:** 1574–8. Correction. *ibid.*; **354:** 780.
3. Lopes P, *et al.* Randomized comparison of intranasal and transdermal estradiol. *Obstet Gynecol* 2000; **96:** 906–12.
4. Davis SR, *et al.* Intranasal versus transdermal matrix oestrogen replacement in Australasian women. *Maturitas* 2005; **51:** 163–71.

TRANSDERMAL ADMINISTRATION. Transdermal estradiol given via *patches* applied to the skin has been reviewed.[1-3] This method of delivery has certain advantages over the oral route in that gastrointestinal and hepatic first-pass metabolism is avoided, liver enzymes are not stimulated (although this may also mean that beneficial effects on serum lipids are absent), and the prolonged drug release from the patch means less frequent application is necessary and hence patient compliance may be improved. For oestrogen replacement in menopausal and postmenopausal women estradiol patches are used continuously or in a cyclical manner, with added progestogen for part of the cycle in those women with an intact uterus. This does not lead to drug accumulation and produces blood-estradiol concentrations and estradiol to estrone ratios similar to those normally observed in premenopausal women. The patch is well tolerated with skin irritation being the main problem. Patches are as effective as oral oestrogens in treating menopausal and postmenopausal symptoms such as flushing and vaginal atrophy and in preventing osteoporosis. Combined HRT patches, providing both estradiol and a progestogen, have also been developed.[4]

Estradiol is also effective when applied topically to the skin as a *gel*[5] or *emulsion*.[6]

1. Balfour JA, Heel RC. Transdermal estradiol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of menopausal complaints. *Drugs* 1990; **40:** 561–82.
2. Cheang A, *et al.* A risk-benefit appraisal of transdermal estradiol therapy. *Drug Safety* 1993; **9:** 365–79.
3. Jewelewicz R. New developments in topical estrogen therapy. *Fertil Steril* 1997; **67:** 1–12.
4. Dando TM, Perry CM. 17 β-Estradiol/levonorgestrel transdermal system. *Treat Endocrinol* 2004; **3:** 319–24.
5. Naunton M, *et al.* Estradiol gel: review of the pharmacology, pharmacokinetics, efficacy, and safety in menopausal women. *Menopause* 2006; **13:** 517–27.
6. Simon JA. ESTRASORB Study Group. Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms. *Menopause* 2006; **13:** 222–31.

Depression. The use of oestrogen therapy in the treatment of premenopausal women with **postnatal** depression has been shown to be effective.[1,2] However, although such therapy could be a useful adjunct to conventional treatment (see Depression, p.373), the risk of serious adverse effects including thrombosis may limit its value.[3]

Whether oestrogens are of benefit in older women, typically with depression associated with the **menopause** (p.2077), is less clear. Some studies of transdermal estradiol have reported benefit,[4-6] whereas other studies of transdermal[7] or oral[8] dosage have not found it to be effective. Whether the presence of a progestogen in combination HRT would reduce any purported benefit is also unclear. Antidepressants remain the standard of care in perimenopausal or postmenopausal women with clinical depression.

1. Gregoire AJP, *et al.* Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996; **347:** 930–3.
2. Ahokas A, *et al.* Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17β-estradiol: a preliminary study. *J Clin Psychiatry* 2001; **62:** 332–6.
3. Dennis CL, *et al.* Oestrogens and progestins for preventing and treating postpartum depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 27/06/08).
4. Soares C de N, *et al.* Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women. *Arch Gen Psychiatry* 2001; **58:** 529–34.
5. Cohen LS, *et al.* Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry* 2003; **160:** 1519–22.
6. Schiff R, *et al.* Short-term transdermal estradiol therapy, cognition and depressive symptoms in healthy older women: a randomised placebo controlled pilot cross-over study. *Psychoneuroendocrinology* 2005; **30:** 309–15.
7. Morrison MF, *et al.* Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 2004; **55:** 406–12.
8. Almeida OP, *et al.* A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: effect on mood, cognition and quality of life. *Neurobiol Aging* 2006; **27:** 141–9.

Gender reassignment. Oestrogens are used in male-to-female transsexuals to develop and maintain secondary sexual characteristics. Although ethinylestradiol and conjugated oestrogens have been used for this purpose, and there is some evidence that such use can improve vascular function,[1] others consider ethinylestradiol too thrombogenic at the doses required [typically 50 to 100 micrograms daily or more] and suggest that estradiol, as the valerate in oral doses of 2 to 4 mg daily, or transdermally as a patch supplying 100 micrograms daily, is the oestrogen of choice.[2,3] Cyproterone acetate is usually also given for its antiandrogenic effect (see p.2089).

1. New G, *et al.* Long-term estrogen therapy improves vascular function in male to female transsexuals. *J Am Coll Cardiol* 1997; **29:** 1437–44.
2. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
3. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.

Growth disorders. Supraphysiological doses of oestrogens inhibit somatic growth and have been used, with a cyclical progestogen, to reduce final height in girls with constitutional tall stature, although such treatment has declined markedly with changing social norms.[1] In early reports, diethylstilbestrol was used, but this is an unsuitable choice because of the increased risk of cancer. Ethinylestradiol has been given in the past in doses of up to 500 micrograms daily, but doses of 50 to 100 micrograms daily came to be preferred, although lower doses may be equally effective.[2,3] Conjugated oestrogens have also been used, and a study[4] reported that doses of 7.5 to 11.25 mg daily resulted in an average decrease of about 5 cm from final predicted height. In practice, doses as low as 625 micrograms daily have been used.[3] Reported height reductions have ranged from 2 to 10 cm but studies are difficult to compare. Treatment has generally been continued until closure of the epiphyses, but the effects of oestrogen therapy may be influenced by both chronological and bone age at the onset of treatment, duration of treatment, the oestrogen used and its dose, and the point of final height assessment.[2] High-dose oestrogen therapy is also associated with adverse effects such as weight gain, headache, nausea, and pigmentation of the areolae or nipples,[2,3] and there can be adverse changes to haemostatic and lipid measures.[2] A retrospective cohort review[5] has also reported that girls who had been treated with high-dose oestrogens were more likely to report fertility problems in later life than similar girls who had not been treated.

Oestrogen therapy has occasionally been used to help promote growth in girls with constitutional delayed puberty (see p.2079).

1. Lee JM, Howell JD. Tall girls: the social shaping of a medical therapy. *Arch Pediatr Adolesc Med* 2006; **160:** 1035–9.
2. Drop SLS, *et al.* Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; **19:** 540–58.
3. Barnard ND, *et al.* The current use of estrogens for growth-suppressant therapy in adolescent girls. *J Pediatr Adolesc Gynecol* 2002; **15:** 23–6.
4. Weimann E, *et al.* Oestrogen treatment of constitutional tall stature: a risk-benefit ratio. *Arch Dis Child* 1998; **78:** 148–51.
5. Venn A, *et al.* Oestrogen treatment to reduce the adult height of tall girls: long-term effects on fertility. *Lancet* 2004; **364:** 1513–18.

Haemorrhagic disorders. Limited evidence supports the use of oestrogens in various bleeding disorders. There have been mixed results from small studies of oestrogens, given alone or with a progestogen, in patients with hereditary haemorrhagic telangiectasia;[1,2] the use of a combined oral contraceptive has been suggested as a suitable option for fertile women with symptomatic epistaxis.[3] There are also some reports[2,4,5] of bleeding being reduced in patients with gastrointestinal vascular malformations from other causes. Conjugated oestrogens have been used in haemorrhagic disorders associated with chronic renal failure and haemorrhagic cystitis (see p.2087).

1. Vase P. Estrogen treatment of hereditary hemorrhagic telangiectasia. *Acta Med Scand* 1981; **209:** 393–6.
2. van Cutsem E, *et al.* Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. *Lancet* 1990; **335:** 953–5.
3. Jameson JJ, Cave DR. Hormonal and antihormonal therapy for epistaxis in hereditary hemorrhagic telangiectasia. *Laryngoscope* 2004; **114:** 705–9.
4. Bronner MH, *et al.* Estrogen-progesterone therapy for bleeding gastrointestinal telangiectasias in chronic renal failure: an uncontrolled trial. *Ann Intern Med* 1986; **105:** 371–4.
5. Siple JF, *et al.* Use of estrogen therapy in a patient with gastrointestinal bleeding secondary to arteriovenous malformations. *Ann Pharmacother* 1997; **31:** 1311–14.

Lactation inhibition. Synthetic oestrogens (e.g. quinestrol) and nonsteroidal oestrogens (e.g. diethylstilbestrol) were historically used to suppress lactation (p.2003). However, this use is now considered inappropriate because of an increased risk of puerperal thromboembolism.

Premenstrual syndrome. Premenstrual syndrome (PMS) presents as a variable combination of psychological and somatic symptoms occurring during the luteal phase of the menstrual cycle, which resolve during, and immediately after, menstruation. Another term, premenstrual dysphoric disorder, has been proposed to cover severe cyclical mood disorder that is functionally incapacitating.[1,2] Whereas about 20 to 40% of women have complaints that may be classified as PMS, only 3 to 8% meet criteria for premenstrual dysphoric disorder.[2] The term premenstrual tension (PMT) has sometimes been applied to the psychological symptoms. Many symptoms of PMS are the same as normal premenstrual symptoms, but are more severe. The aetiology of PMS is not fully understood, although it is thought that affected women may be more sensitive to the effects of normal hormonal fluctuations on CNS neurotransmitter function.[2]

Initial management includes non-medical interventions[3] such as education and support, counselling, stress management, relaxation techniques, and exercise; caffeine and salt restriction are of unproven benefit. The herbal remedy agnus castus has been found to be of benefit.[4] For patients with moderate to severe symptoms, a number of drugs have been tried with varying degrees of success; objective assessment of efficacy has been hampered by varying diagnostic criteria, a marked placebo response, and difficulties in obtaining reproducible responses. Treatment may be aimed at modifying the menstrual cycle or treating specific symptoms.

In women with mainly psychological symptoms, *SSRIs* can be helpful.[1,3,5,6] Fluoxetine and sertraline have been shown in controlled studies to alleviate both psychological and somatic symptoms in women with PMS, and may be given intermittently (only in the luteal phase) or continuously. If treatment with one SSRI is ineffective or not tolerated, another SSRI or *venlafaxine* may be substituted.[1,3,6] There is limited information on the use of SSRIs for PMS in adolescents, and precautions regarding suicidal ideation in young adults should be considered.[2] *Clomipramine*, a nonselective serotonin reuptake inhibitor, has been tried for PMS with some success. The anxiolytic *alprazolam* has also been used, but use of this and other benzodiazepines should be restricted to the luteal phase of the cycle in selected patients to minimise the risk of dependence and tolerance.[7]

Abdominal bloating and swelling associated with PMS has traditionally been thought to be due to sodium and water retention. However, in most women with these symptoms there is no evidence of an increase in body-weight or in body sodium or total water, and use of *diuretics* is therefore not justified.[8] Nevertheless, in women with appreciable weight gain and abdominal bloating in the luteal phase, the aldosterone antagonist spironolactone may be useful.[1,6,9] Another symptom of PMS, cyclical mastalgia, is discussed on p.2092.

Pyridoxine has been tried on the basis that it is a cofactor in neurotransmitter (specifically serotonin) synthesis, and has been found to relieve depression induced by oral contraceptives in selected patients. However, its efficacy in PMS is equivocal, and high daily doses have been associated with neurotoxicity.[10] *Calcium* supplementation may relieve symptoms of PMS.[6,11]

Treatments that modify the menstrual cycle have often been used in women with PMS. In general, drugs with proven efficacy such as danazol, oestrogen implants, and gonadorelin analogues are reserved for women with severe PMS unresponsive to other treatments, because of their adverse effects. *Progestogen* therapy was once popular, but beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground. In addition, a systematic review[12] of clinical trials found no evidence to support the use of progesterone or progestogens for PMS. *Combined oral contraceptives* have met with limited success.[2] They may be useful in some women for the control of somatic symptoms, but in others, PMS is caused or exacerbated by them. There is some suggestion that combined contraceptives containing drospirenone may be more effective in managing PMS than those containing progestogens such as levonorgestrel or norethisterone.[3] Consideration should be given to continuous rather than cyclical use.[3] Perimenopausal women may benefit from *oestrogen* delivered from transdermal patches. In women with a uterus, use with a cyclical progestogen is required to avoid endometrial hyperplasia; unfortunately, the progestogen may be associated with the return of symptoms. Possible strategies to minimise this include the use of a less androgenic progestogen, reducing the frequency with which it is given, or using an intra-uterine device to deliver the progestogen locally.[13] *Danazol* can be useful,[1,3] but there is concern over its adverse effects on lipids during long-term use and over the risk of masculinisation of a female fetus should pregnancy occur. For patients with severe symptoms not amenable to other treatments, gonadorelin analogues such as *goserelin* can be used to eliminate ovarian function, 'add-back' treatment with oestrogen plus progestogen being given to protect against the adverse effects of oestrogen deficiency including osteoporosis.[3] This treatment is very effective for both physical and psychological symptoms.[14] Short-term use (3 months) of a gonadorelin analogue alone has been used to confirm the diagnosis of PMS, or to predict the response to bilateral oophorectomy.[1,3]

1. Johnson SR. Premenstrual syndrome, premenstrual dysphoric disorder, and beyond: a clinical primer for practitioners. *Obstet Gynecol* 2004; **104:** 845–59.
2. Braverman PK. Premenstrual syndrome and premenstrual dysphoric disorder. *J Pediatr Adolesc Gynecol* 2007; **20:** 3–12.
3. Royal College of Obstetricians and Gynaecologists. Management of premenstrual syndrome (Green-top guideline 48, issued December 2007). Available at: http://www.rcog.org.uk/resources/Public/pdf/green_top48_pms.pdf (accessed 27/06/08)
4. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001; **322:** 134–7.
5. Wyatt KM, *et al*. Selective serotonin reuptake inhibitors for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 27/06/08).
6. Halbreich U. Algorithm for treatment of premenstrual syndromes (PMS): experts' recommendations and limitations. *Gynecol Endocrinol* 2005; **20:** 48–56.
7. Severino SK, Moline ML. Premenstrual syndrome: identification and management. *Drugs* 1995; **49:** 71–82.
8. O'Brien PMS. Helping women with premenstrual syndrome. *BMJ* 1993; **307:** 1471–5.
9. Mortola JF. A risk-benefit appraisal of drugs used in the management of premenstrual syndrome. *Drug Safety* 1994; **10:** 160–9.
10. Wyatt KM, *et al*. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ* 1999; **318:** 1375–81.
11. Thys-Jacobs S, *et al*. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1998; **179:** 444–52.
12. Wyatt K, *et al*. Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; **323:** 776–80.
13. Hassan I, *et al*. PMS in the perimenopause. *J Br Menopause Soc* 2004; **10:** 151–6.
14. Wyatt KM, *et al*. The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. *BJOG* 2004; **111:** 585–93.

Preparations

BP 2008: Estradiol and Norethisterone Acetate Tablets; Estradiol and Norethisterone Tablets; Estradiol Injection; Estradiol Transdermal Patches; ***USP 31:*** Estradiol and Norethindrone Acetate Tablets; Estradiol Cypionate Injection; Estradiol Injectable Suspension; Estradiol Pellets; Estradiol Tablets; Estradiol Transdermal System; Estradiol Vaginal Cream; Estradiol Valerate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Aerodiol; Climaderm†; Disequens; Estraderm; Estradot; Estreva†; Estring†; Estrofem; Etrosteron; Eutocol; Evorel; Fem 7†; Ginatex; Ginediol; Hormodiol; Lindisc; Oestro Gel; Progynon; Progynova; Replasyn†; Ronfase; Rontagel; Transdiol†; Trial Gel; Trial Sat; ***Austral.:*** Aerodiol; Climara; Dermestril†; Estraderm; Estradot; Estrofem; Femtran; Menorest; Primogyn Depot; Progynova; Sandrena; Vagifem; Zumenon; ***Austria:*** Aerodiol; Climara; Cycloderm; Dermestril; Duokliman; Estracutan; Estraderm; Estradot; Estramon; Estring; Estrofem; Estrogel; FemSeven; FemSieben; Klimapur; Klimaredukt; Linoladiol; Menorest; Merimono; Progynon; Progynova; Sterigin; Systen; Vagifem; Zerella†; Zumenon; ***Belg.:*** Aerodiol; Climara; Dermestril; Estraderm; Estreva; Estrofem; Feminova; Meno-Implant; Oestrogel; Progynova; Systen; Vagifem; Vivelle; Zumenon; ***Braz.:*** Aerodiol; Avaden; Avicis; Benzo-Ginoestril; Climaderm; Estradelle; Estraderm†; Estradot; Estreva; Estrofem; Fem 7; Ginedisc†; Hormodose; Lindisc; Menorest†; Merimono; Natifa; Oestrogel; Primogyna; Riselle; Sandrena; Systen; ***Canad.:*** Climara; Delestrogen†; Estrace; Estraderm; Estradot; Estring; Estrogel; Oesclim; Vagifem; Vivelle†; ***Chile:*** Climaderm; Cyclobiol†; Dermatrans; Enadiol; Epiestrol; Estranova E; Estreva; Farlutes; Fem 7; Femalon; Femiderm; Femidot; Ginoderm; Mirion; Oesclim†; Primaquin; Primofol Depot†; Primogyna†; Progynova; Sandrena; Transvital; Vagifem; ***Cz.:*** Agofollin; Climara; Dermestril; Divigel; Ellestе†; Estrace†; Estraderm; Estradot; Estrahexal; Estrapatch; Estreva†; Estrimax; Estring†; Estrofem; Fem 7†; Linoladiol N; Menorest†; Neofollin; Octodiol; Oesclim†; Oestrogel; Riselle; Systen; Vagifem; ***Denm.:*** Aerodiol; Climara; Divigel; Estraderm†; Estring; Estrofem; Estrogel; Evorel; Femanest; Progynon; Sandrena; Vagifem; Vivelle Dot; ***Fin.:*** Climara; Dermestril; Divigel; Estraderm†; Estradot; Estrena; Estring; Estrofem; Estrogel; Evorel; FemSeven; Menorest†; Merimono; Progynova; Vagifem; Zumenon; ***Fr.:*** Aerodiol; Climara; Delidose; Dermestril; Estraderm; Estrapatch; Estrofem; Evafilm†; Menorest; Oesclim; Oestrodose; Oestrogel; Oromone; Progynova; Provames; Systen; Thais; Vivelledot; ***Ger.:*** Aerodiol; Cerella†; Cutanum; Dermestril; Ephelia†; Estrabeta; Estraderm; Estradot; Estramon; Estreva; Estrifam; Estring; Estronorm; Evorel†; Fem 7; Femoston mono; Gynokadin; GynPolar; Linoladiol N; Menorest†; Merimono; Progynon Depot 10†; Progynova; Sandrena; Sisare mono; Tradelia; Vagifem; ***Gr.:*** Aerodiol†; Dermestril; Estraderm TTS†; Estradot; Estramon; Estring†; Estrofem†; Estrogel; Menorest; Oesclim†; Oestrogel; Vagifem; ***Hong Kong:*** Aerodiol†; Dermestril; Estraderm; Estreva; Estrofem; Fem 7†; Oestrogel; Progynova; Vagifem; ***Hung.:*** Calidiol; Dermestril; Divigel; Estraderm; Estradot†; Estramon; Estrapatch; Estrimax; Estrofem; FemSeven; Linoladiol N; Oesclim†; Oestrogel; Systen†; Vagifem; ***India:*** Divigel; Estraderm†; ***Indon.:*** Estreva; Fem 7; Progynova; ***Irl.:*** Aerodiol; Climara; Dermestril†; Divigel; Epiestrol†; Estraderm; Estradot; Estrofem; Evorel; Fematab; Menorest†; Oestrogel†; Vagifem; ***Israel:*** Dermestril; Estraderm; Estrofem; Evorel; Meno-Patch†; Oestrodose; Oestrogel; Progynova; Vagifem; ***Ital.:*** Aerodiol; Armonil; Climara; Dermestril; Ephelia; Epiestrol; Esclima; Estraderm; Estroclim; Estrodose; Estrofem; FemSeven; Gelestra; Ginaikos; Menorest; Progynova; Sandrena; Sprediol; Systen; Vagifem; Zerella; ***Malaysia:*** Divigel; Estrofem†; Oestrogel; Progynova; Trisequens†; ***Mex.:*** Armistor; Benzo-Ginestryl; Climaderm; Essventia; Estraderm; Estramon; Estreva; Evorel; Fem 7; Ginedisc; Oestrogel; Primogyn; Sandrena; Systen; ***Mon.:*** Femsept; ***Neth.:*** Aerodiol; Climara; Dermestril; Estraderm; Estradot; Estreva; Estrofem; Fem 7; Femring†; Meno-Implant; Menorest; Ovestal; Progynova; Sandrena; Systen; Vagifem; Zumenon; ***Norw.:*** Climara; Estraderm†; Estradot; Estring; Evorel; Progynova; Vagifem; ***NZ:*** Aerodiol; Climara; Estraderm; Estrofem; Femtran; Progynova; Sandrena†; Vagifem; ***Philipp.:*** Climara; Estrofem; Progynova; Vagifem; ***Pol.:*** Calidiol; Climara; Divigel; Estraderm; Estradot; Estrapatch; Estreva; Estrofem; Estroplast; Fem 7; Oesclim; Progynova; Systen; Vagifem; ***Port.:*** Climara; Crinohermal; Dermestril; Epiestrol; Estraderm; Estradot; Estrapatch; Estreva; Estrofem; Estronar†; Feminova; Femring; Femsete; Menorest†; Vagifem; Zumenon; ***Rus.:*** Climara (Климара); Divigel (Дивигель); Estrimax (Эстримакс); Estrofem (Эстрофем); Oestrogel (Эстрожель); Progynova (Прогинова); ***S.Afr.:*** Climara; Estraderm; Estradot; Estring; Estro-Pause; Estrofem; Evorel; Femigel; Primogyn Depot; Progynova; Vagifem; ***Singapore:*** Divigel; Estraderm; Estreva; Estrofem; Fem 7†; Oestrogel†; Progynova; Vagifem; ***Spain:*** Absorlent; Alcis; Cliogan; Dermestril; Endomina; Esprasone; Estraderm; Estradot; Estroffik; Evopad; Menorest†; Meriestra; Oestraclin; Oestrodose†; Progynova; Vagifem; ***Swed.:*** Climara; Divigel; Estraderm†; Estradot; Evorel; Femanest; FemSeven; Menorest†; Oesclim; Oestring; Progynon; Vagifem; ***Switz.:*** Aerodiol; Cerina†; Climara; Dermestril†; Divigel; Epiestrol†; Estraderm; Estradot; Estramon; Estreva†; Estring; Estrofem N; Fem 7; FemSeven†; Menorest†; Oestrogel; Progynova; Sandrena; Systen; Vagifem; Zumenon; ***Thai.:*** Climara; Divigel; Estrofem; Oestrogel; Progynon; Progynova; Vagifem; ***Turk.:*** Aerodiol; Akrofolline; Climara; Estraderm; Estramon; Estreva; Vagifem; ***UK:*** Aerodiol†; Bedol; Climaval; Elleste-Solo; Estraderm; Estradot; Estring; Evorel; Fematrix; FemSeven; FemTab†; Menorest†; Menoring†; Oestrogel; Progynova; Sandrena; Vagifem; Zumenon; ***USA:*** Alora; Climara; Delestrogen; depGynogen; Depogen; Divigel; Elestrin; Esclim; Estrace; Estraderm; Estrasorb; Estring; Estrogel; Evamist; FemPatch; Femring; Femtrace; Gynodiol; Menostar; Vagifem; Valergen; Vivelle; ***Venez.:*** Aerodiol; Climaderm; Estraderm†; Estradot; Estrogel; FemSeven; Progynova.

Multi-ingredient: ***Arg.:*** Activelle; Angeliq; Atrimon; Ciclocur; Climene; Cristerona; Dilena†; Dos Dias N; Equifem; Estalis; Estalis Sequi; Estracomb; Estragest; Evorel Conti; Evorel Sequi; Farludiol; Farludiol Ciclo; Fem 7 Combi†; Fempack; Gadofem; Gynodian Depot; Hosterona; Kliogest; Lubriderm; Menstrogen; Mesigyna; Perlutal; Plenifem†; Prefest; Primosiston; Supligol NF; Supligol†; Totelle Ciclico; Totelle Continuo; Trial Combi; Trial Gest; Trial Pack†; Trisequens; ***Austral.:*** Angeliq; Climen; Estalis Continuous; Estalis Sequi; Estracombi; Femoston; Kliogest; Kliovance; Trisequens; ***Austria:*** Activelle; Allurene; Angeliq; Climabelle†; Climen; Climodien; Cyclacur; Estalis; Estalis Sequens; Estracomb; Femipak; Femoston; Femoston Conti; Femphascyl; Femphascyl conti; FemSeven Combi; Filena†; Gynodian Depot; Ichth-Oestren; Kliogest; Lafamme; Liseta†; Mericomb; Merigest; Miniquе†; Novofem; Perikliman; Trisequens; ***Belg.:*** Activelle; Angeliq; Climen; Climodien; Cyclocur; Dimenformon; Diviplus; Diviva; Estalis; Estracombi; Feminova Plus; Femoston; Femoston Conti; Kliogest; Novofem; Totelle Cycle†; Trisequens; Trivina†; ***Braz.:*** Activelle; Angeliq; Cicloprimogyna; Cliane; Climene; Cyclofemina; Dilena; Elamax; Estalis; Estalis SQ; Estandron P; Estracomb†; Estragest; Femineo†; Femoston; Femoston Conti; Gestadinona; Gineane; Ginecosidе†; Ginedisc 50 Plus†; Kliogest; Lindisc Duo†; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Normomensil†; Perlutan; Postoval†; Prefest; Preg-Less; Suprema; Systen Conti; Systen Sequi; Totelle; Totelle Ciclo; Trinestril; Trisequens; Unalmes†; Uno-Ciclo†; ***Canad.:*** Climacteron; Estalis; Estalis Sequi; Estracomb; ***Chile:*** Activelle; Agurin†; Angeliq; Avaden; Cliane; Climene; Cyclofem†; Enadiol CC; Enadiol MP; Enadiol Neta; Estandron Prolongado; Estracomb; Estragest; Estranova 30 Simple; Estranova CC; Farlupost; Fem 7 Combi; Femoston; Femoston Conti; Ginefolin; Gravidinona†; Gynodian Depot; Kilios; Kliogest; Mesigyna; Novafem; Postoval†; Primaquin MP; Primaquin MP Continuo; Progyluton; Totelle; Totelle Continuo; Trisequens; Unalmes; ***Cz.:*** Activelle; Aknefug†; Alpicort F; Angeliq; Avaden†; Climara Duo†; Climen; Convaden†; Cyclo-Menorette†; CycloOstrogynal†; Divina; Diviseq; Estalis; Estalis Sequi; Estrace Plus†; Estrace-C†; Estracomb†; Estragest†; Femoston; Femoston Conti; Folivirin; Gynodian Depot; Indivina; Kliane; Klimodien; Klimonorm; Kliogest; Linoladiol-H N†; Novofem; Pausogest; Sequidot; Systen Conti; Systen Sequi; Triaklim†; Trisequens; ***Denm.:*** Activelle; Angemin; Climen; Climodien; Cyclo-Progynon; Divina; Divina Plus; Estracomb; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Indivina; Klimalet; Klimaxil†; Kliogest; Novofem; Nuvelle; Ostranorm†; Totelle†; Trevina; Trinorm†; Trisekvens; ***Fin.:*** Activelle; Angeliq; Climara Duo†; Cyclabil; Divina; Divitren; Estalis; Estalis Sekvens; Estracomb†; Evorel Conti; Evorel Sequi; Femilar; Femoston; Femoston Conti; FemSeven Combi; Indivina; Kliogest; Mericomb; Merigest; Novofem; Senikolp†; Totelle Sekvens†; Trisekvens; ***Fr.:*** Activelle; Angeliq; Avadene; Climaston; Climene; Climodiene; Divina; Diviseq; Duova; Kliogest; Novofemme; Successia†; Trisequens; ***Ger.:*** Activelle; Aknefug-Emulsion†; Alpicort F; Androfemon†; Angeliq; Climen; Climodien; Clionara; Crinohermal fem; Cyclo-Menorette; Cyclo-Progynova; CycloOstrogynal; Estalis Sequi; Estracomb†; Estrafemol; Estragest; Fem 7 Combi; Femoston; Femoston Conti; Gianda; Gravibinon†; Gynamon; Gynodian Depot; Indivina; Jephagynon†; Klimonorm; Kliogest N; Lafamme; Linoladiol-H N; Mericomb; Merigest; NeoOstrogynal†; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; Novofem; Osmil; Ostronara; Procyclo; Sisare; Sisare 28; Syngynon†; Trisequens; Vitrena†; ***Gr.:*** Activelle†; Angeliq; Climodien†; Cyclacur; Divina; Estalis; Estopause; Estracomb TTS; Femaston; Kliogest; Nuvelle†; Systen Conti; Systen Sequi; Trisequens; ***Hong Kong:*** Activelle; Angeliq; Climen 28; Dilena; Estracomb; Femoston; Hormonin; Klimonorm†; Kliogest; Novofem; Trisequens; ***Hung.:*** Activelle; Alpicort F; Angeliq; Climen; Cyclo-Menorette†; Divina; Divitren†; Estracomb; Estragest; Femoston; FemSeven Combi; Indivina; Klimodien†; Klimonorm; Kliogest; Linoladiol-H N†; Pausogest; Triaklim; Trisequens; Tulita; ***India:*** Kemicetine Antiozena; Mixogen; ***Indon.:*** Angeliq; Climen 28; Cyclo-Progynova; Cyclofem; Mediol; Renodiol; ***Irl.:*** Activelle; Angeliq; Diviseq†; Estalis; Estalis Sequi; Estracombi; Estrapak†; Evorel Conti; Femoston; Femoston Conti; Indivina; Kliogest; Novofem; Nuvelle†; Trisequens; ***Israel:*** Activelle; Angeliq; Evorel Conti; Evorel Sequi; Kliogest; Meno-MPA†; Meno-Net†; Novofem; Progyluton; Trisequens; ***Ital.:*** Activelle; Angeliq; Biormon†; Climen; Combiseven; Estalis Sequi; Estracomb; Femity; Femoston; Femoston Conti; Filena; Gravibinan†; Gynodian Depot; Kliogest; Menovis; Naemis; Nuvelle; Nuvelle TS†; Pausene; Totelle†; Trisequens; ***Malaysia:*** Activelle; Climen; Duogynon; Femoston; Femoston Conti; Klimonorm†; Kliogest†; Progyluton; ***Mex.:*** Anafertin; Angeliq; Avaden; Binodian; Cliane; Climene; Cyclofemina; Damax; Despamen; Dilena; Estalis; Estracomb; Evorel Conti; Genofort; Ginoplant†; Gravidinona; Lutalmin; Lutoginestryl F; Mesigyna; Metrigen Fuerte; Nostidyn; Ominol†; Patector; Perludil; Perlutal; Prefest; Primosiston†; Primoson-F; Progediol†; Proger-F; Progyluton; Totelle Continuo; Totelle Secuencial; Xofemina; Yectames; ***Mon.:*** FemseptCombi; Naemis; ***Neth.:*** Activelle; Allurene; Angeliq; Avaden†; Climaston Continu; Climene; Climodien; Cyclocur; Divina†; Estalis; Estalis Sequi; Estandron Prolongatum; Estracomb; Fem 7 Sequi; Femoston; Femoston Continu; Femphascyl Continu; Kliogest; Lafamme; Naemis; Novofem; Trisequens; ***Norw.:*** Activelle; Climen†; Climodien; Cyclabil; Diviseq†; Estalis; Estalis Sekvens; Indivina; Kliogest; Novofem; Totelle Sekvens†; Trisekvens; ***NZ:*** Cliane; Estrapak†; Kliogest; Kliovance; Nuvelle; Trisequens; ***Philipp.:*** Angeliq; Climen 28; Femoston; Kliogest; ***Pol.:*** Activelle; Alpicort E; Angeliq; Climen; Cyclo-Progynova; Divina; Diviseq; Estalis; Estalis Sequi; Estracomb; Fem 7 Combi; Femoston; Femoston Conti; Gynodian Depot; Indivina; Klimonorm; Kliogest; Novofem; System Conti; Systen Sequi; Trisequens; ***Port.:*** Activelle; Angeliq; Avadene; Cicnor†; Climara Duo†; Climen; Climodien; Dilena; Emmenovis†; Estalis; Estalis Sequi; Estracomb; Femoston; Femoston 1/5; Femsete Combi; Femsete Evo; Kliogest; Lafamme; Naemis; Novofem; Nuvelle; Progyluton; Trisequens; ***Rus.:*** Angeliq (Анжелик); Climen (Климен); Climodien (Климодиен); Cyclo-Progynova (Цикло-прогинова); Divina (Дивина); Diviseq (Дивисек); Divitren (Дивитрен); Femoston (Фемостон); Femoston 1/5 (Фемостон 1/5); Gynodian Depot (Гинодиан Депо); Indivina (Индивина); Klimonorm (Климонорм); Pausogest (Паузогест); Triaklim (Триаклим); Trisequens (Трисеквенс); ***S.Afr.:*** Activelle; Angeliq; Climen; Divina; Estracombi; Estro-Pause N; Evorel Conti; Evorel Sequi; Femoston; Femoston Conti; Kliogest; Mixogen; Novofem; Postoval; Prefesta; Primodian Depot; Trisequens; Trivina; ***Singapore:*** Activelle; Climen; Estracomb; Femoston; Femoston Conti; Kliogest; Progyluton; Trisequens; ***Spain:*** Absorlent Plus; Activelle; Angeliq; Auroclim; Climen; Climodien; Clisin†; Duofemme; Endomina Plus; Estalis; Estalis Sequi; Estracomb; Merigest; Merigest Sequi; Mevaren; Nuvelle; Perifem; Progyluton; Topasel; Trisequens; ***Swed.:*** Activelle; Angemin; Climodien; Cyclabil; Divina Plus; Divina†; Estalis; Estalis Sekvens; Estracomb†; Evorel Micronor; Femanor; Femasekvens; Indivina; Kliogest; Novofem; Totelle Sekvens†; Totelle†; Trisekvens; Trivina; ***Switz.:*** Activelle; Alpicort F; Climen; Cyclacur; Diviseq; Estalis; Estalis Sequi; Estracomb; Estragest; Fem 7 Combi; Femoston; Femoston Conti; Gynodian Depot; Indivina; Kliogest N; Linoladiol†; Mericomb; Merigest; Novofem; OestroTabs Plus Cyclic†; Primosiston†; Systen Conti; Systen Sequi; Trianal; Trisequens; ***Thai.:*** Activelle; Angeliq; Climen; Cyclo-Progynova; Diviseq; Duoton; Femoston 1/10; Femoston Conti; Indivina; Klimonorm; Phenokinon-F; Primodian Depot; ***Turk.:*** Activelle; Angeliq; Climen; Climodien; Cyclo-Progynova; Di-Pro; Divina; Estandron Prolongatum; Estracombi; Kliogest; Mesigyna; Trisequens; ***UK:*** Angeliq; Climagest; Climesse; Clinorette; Cyclo-Progynova 1 mg; Cyclo-Progynova 2 mg; Elleste Duet Conti; Elleste-Duet; Estracombi; Estrapak†; Evorel Conti; Evorel Pak†; Evorel Sequi; Femapak; Femoston; Femoston Conti; FemSeven Conti; FemSeven Sequi; FemTab Continuous†; FemTab Sequi†; Hormonin; Indivina; Kliofem; Kliovance; Novofem; Nuvelle; Nuvelle Continuous; Tridestra; Trisequens; ***USA:*** Activella; Angeliq; ClimaraPro; CombiPatch; Depo-Testadiol; Depotestogen; Lunelle†; Prefest; ***Venez.:*** Avaden; Cliane; Climene; Estracomb†; Estragest; Femoston; Femoston Conti; Ginecosid; Gynodian Depot; Mesigyna; Primosiston†; Progyluton; Totelle Ciclico; Totelle Continuo.

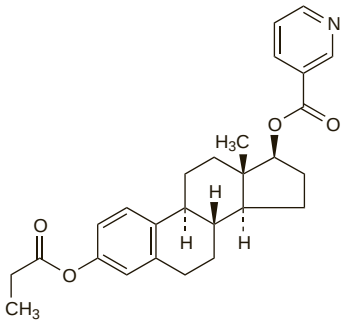
Estrapronicate *(rINN)*

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 an anabolic steroid and a progestogen for osteoporosis.

Estriol *(BAN, rINNM)*

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

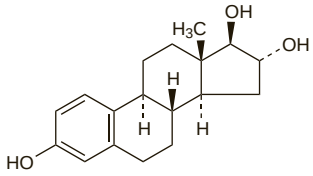
Эстриол

$C_{18}H_{24}O_3$ = 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, rINNM)*

Estriol, Succinate Sodique d'; Estrioli Natrii Succinas; Oestriol Sodium Succinate; Succinato sódico de estriol. Disodium 3-hydroxyestra-1,3,5(10)-triene-16α,17β-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; Estriolsuccinat; Oestriol Succinate; Succinato de estriol. 3-Hydroxyestra-1,3,5(10)-triene-16α,17β-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; Orgestriol; ***Austral.:*** Ovestin; ***Austria:*** Ortho-Gynest; Ovestin; Styptanon; ***Belg.:*** Aacifemine; Ortho-Gynest; ***Braz.:*** Estriopax; Hormocervix; Hormoniol; Ovestrion; Styptanon; ***Chile:*** Ovestin; Sinapause; Vacidox; ***Cz.:*** Ortho-Gynest; Ovestin; ***Denm.:*** Ovestin; ***Fin.:*** Ovestin; Pausanol; ***Fr.:*** Gydrelle; Physiogine; Trophicreme; ***Ger.:*** Cordes Estriol; Gynasan†; OeKolp; Oestro-Gynaedron M; Ortho-Gynest; Ovestin; Synapause E; Xapro; ***Gr.:*** Ovestin; ***Hong Kong:*** Ovestin†; ***Hung.:*** Estrokad; Ortho-Gynest; Ovestin; ***India:*** Evalon; ***Indon.:*** Ovestin; ***Irl.:*** Ortho-Gynest†; ***Israel:*** Ortho-Gynest; Ovestin; ***Ital.:*** Colpogyn; Ortho Gynest Depot; Ovestin; Trofogin; ***Jpn:*** Estriel; ***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 (Овестин); ***S.Afr.:*** Synapause; ***Spain:*** Ovestinon; ***Swed.:*** Ovesterin; ***Switz.:*** Oestro-Gynaedron Nouveau; Ortho-Gynest; Ovestin; ***Thai.:*** Ovestin†; ***Turk.:*** Estrofem; 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; Foliculina; Follicular Hormone; Folliculin; Ketohydroxyoestrin; Oestrone; Östron. 3-Hydroxyestra-1,3,5(10)-trien-17-one.

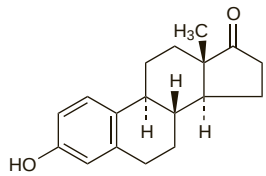
Эстрон

$C_{18}H_{22}O_2$ = 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.:*** Gineburno†; ***Fin.:*** Senikolp†; ***Fr.:*** Synergon; ***Hong Kong:*** Hormonin; ***Spain:*** Cicatral; Grietalgen; Grietalgen Hidrocort†; ***Thai.:*** Metharmon-F; ***Turk.:*** Synergon; ***UK:*** Hormonin.

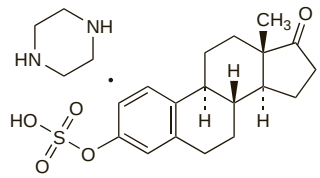
Estropipate *(BAN)*

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

Эстропипате

$C_{18}H_{22}O_5S.C_4H_{10}N_2$ = 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)*

Aethinyloestradiolum; Ethinyl Estradiol; Éthinylestradiol; Ethinylestradiolum; Ethinyloestradiol; Etinilestradiol; Etinilestradiolis; Etinilöstradiol; Etinilösztradiol; Etinylestradiol; Etinyliestradioli; Etynyloestradiol; NSC-10973. 17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol; 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol.

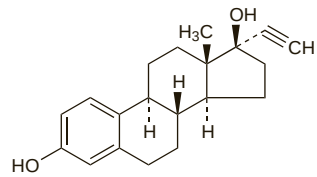
Этинилэстрадиол

$C_{20}H_{24}O_2$ = 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.