primary ovarian failure. The usual oral dose is 50 mg of clomifene citrate daily for 5 days, starting on or about the 5th day of the menstrual cycle or at any time if there is amenorrhoea. If ovulation does not occur, a course of 100 mg daily for 5 days may be given starting as early as 30 days after the previous one. Women should be examined for pregnancy and ovarian enlargement or cysts between treatment cycles. In general, 3 courses of therapy are adequate to assess whether ovulation is obtainable. If ovulation has not occurred, the diagnosis should be re-evaluated. Once ovulation is established, each treatment cycle of clomifene should be started on or about the 5th day of the menstrual cycle. If pregnancy has not occurred after a total of about 6 treatment cycles, licensed product information recommends that no further clomifene therapy should be given (but see also Carcinogenicity, above). Clomifene has also been used with gonadotrophins.

Clomifene has been used in the treatment of male infertility due to oligospermia to stimulate gonadotrophin release and enhance spermatogenesis, but there is limited convincing evidence of benefit.

Infertility. Reviews.

1. Homburg R. Clomiphene citrate—end of an era? a mini-review. *Hum Reprod* 2005; **20:** 2043–51.
2. Cèdrin-Durnerin I. Contre l'utilisation du citrate de clomifène dans les infertilités inexpliquées. *Gynecol Obstet Fertil* 2006; **34:** 61–5.
3. Merviel P. Pour une utilisation raisonnable du citrate de clomifène dans les infertilitiés inexpliquées. *Gynecol Obstet Fertil* 2006; **34:** 66–9.
4. The Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. *Fertil Steril* 2006; **86** (5 suppl): S187–S193.

Preparations

BP 2008: Clomifene Tablets;
USP 31: Clomiphene Citrate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Genozym; Serofene; ***Austral.:*** Clomhexal; Clomid; Fermil; Serophene; ***Austria:*** Serophene; ***Belg.:*** Clomid; Pergotime; ***Braz.:*** Clomid; Indux; Serophene; ***Canad.:*** Clomid; Serophene; ***Chile:*** Serofene†; Zimaquin; ***Cz.:*** Clomhexal; Clostilbegyt; Serophene†; ***Denm.:*** Pergotime; ***Fin.:*** Clomifen; ***Fr.:*** Clomid; Pergotime; ***Ger.:*** Clomhexal; ***Gr.:*** Serpafar; ***Hong Kong:*** Clomid†; Clostilbegyt; Duinum†; Fertilan; Ova-Mit; Serophene; ***Hung.:*** Clostilbegyt; Serophene†; ***India:*** Clofert; Clopreg; Fertomid; Ovipreg; Ovofar; Siphene; ***Indon.:*** Blesifen; Clomifil; Clovertil; Fensipros; Fertilphen; Fertin; Genoclom; Mestrolin; Ofertil; Pinfetil; Profertil; Provula; ***Irl.:*** Clomid; ***Israel:*** Ikaclomin; ***Ital.:*** Clomid; Prolifen; Serofene; ***Malaysia:*** Clomid; Clostilbegyt; Duinum; Ova-Mit; Ovinum; Phenate; Serophene†; ***Mex.:*** Omifin; Serophene†; ***Neth.:*** Clomid; Serophene; ***Norw.:*** Pergotime; ***NZ:*** Phenate; Serophene; ***Philipp.:*** Clomid; Clostil; I-Clom; Ova-Mit; ***Pol.:*** Clostilbegyt; ***Port.:*** Dufine; ***Rus.:*** Clostilbegyt (Клостилбегит); ***S.Afr.:*** Clomid; Clomihexal; Fertomid; Serophene†; ***Singapore:*** Clomid; Clostilbegyt; Duinum; Ova-Mit; Ovinum; Phenate†; Serophene; ***Spain:*** Clomifeno†; Omifin; ***Swed.:*** Pergotime; ***Switz.:*** Clomid; Serophene; ***Thai.:*** Clomid; Duinum; Ova-Mit; Ovinum; Serophene; ***Turk.:*** Fertilin; Gonaphene; Klomen; Serophene; ***UK:*** Clomid; ***USA:*** Clomid; Serophene; ***Venez.:*** Serophene.

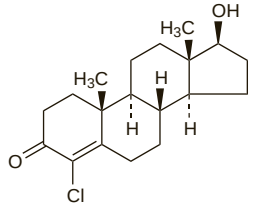
Clostebol Acetate *(BAN, rINNM)* ⊗

Acetato de clostebol; 4-Chlorotestosterone Acetate; Chlortestosterone Acetate; Clostébol, Acétate de; Closteboli Acetas. 4-Chloro-3-oxoandrost-4-en-17β-yl acetate; 4-Chloro-17β-hydroxyandrost-4-en-3-one acetate.

Клостебола Ацетат

$C_{21}H_{29}ClO_3$ = 364.9.

CAS — 1093-58-9 (clostebol); 855-19-6 (clostebol acetate).



(clostebol)

Profile

Clostebol acetate has anabolic properties (see Testosterone, p.2129) and has been given by intramuscular injection and orally. It has also been applied topically to wounds and ulcers, and has been used as an ophthalmological preparation.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Trofodermin; ***Ger.:*** Megagrisevit†; ***Mex.:*** Trofodermin-S†.

Multi-ingredient: ***Braz.:*** Novaderm; Trofodermin; ***Chile:*** Trofodermin Neomicina; ***Ital.:*** Trofodermin; ***Mex.:*** Neobol; ***Thai.:*** Trofodermin†.

Conjugated Oestrogens

Conjugated Estrogens; Estrogeenit, konjugoidut; Estrogena Coniugata; Estrogenai, konjuguoti; Estrogener, konjugerade; Estrogènes conjugués; Estrogeni Coniunct; Estrogeni coniuncti; Estrógenos conjugados; Estrogeny konjugované; Konjugált ösztrogének; Konjüge Östrojen.

Эстрогены Коньюгированные

ATC — G03CA57.

ATC Vet — QG03CA57.

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

Ph. Eur. 6.2 (Estrogens, Conjugated). A mixture of various conjugated forms of oestrogens obtained from the urine of pregnant mares or by synthesis, dispersed in a suitable powdered diluent. It contains two principal components, 52.5 to 61.5% of sodium estrone sulfate and 22.5 to 30.5% of sodium equilin sulfate; the total of the combined two is 79.5 to 88.0%. It also contains 2.5 to 9.5% of sodium 17α-estradiol sulfate, 13.5 to 19.5% of sodium 17α-dihydroequilin sulfate, and 0.5 to 4.0% of sodium 17β-dihydroequilin sulfate. All percentages are related to the labelled content.

An almost white brownish amorphous powder.

USP 31 (Conjugated Estrogens). A mixture of sodium estrone sulfate and sodium equilin sulfate, derived wholly or in part from equine urine or synthetically from estrone and equilin. It contains other conjugated oestrogenic substances of the type excreted by pregnant mares. It contains 52.5 to 61.5% of sodium estrone sulfate and 22.5 to 30.5% of sodium equilin sulfate; the total of the two combined should comprise 79.5 to 88.0% of the labelled content of conjugated oestrogens. It should contain, as sulfate conjugates, 13.5 to 19.5% of 17α-dihydroequilin, 2.5 to 9.5% of 17α-estradiol, and 0.5 to 4.0% of 17β-dihydroequilin, relative to the labelled content of conjugated oestrogens.

If it is obtained from natural sources it is a buff-coloured amorphous powder which is odourless or has a slight characteristic odour; the synthetic form is a white to light buff-coloured crystalline or amorphous powder, odourless or with a slight odour. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Synthetic Conjugated Estrogens, A

Synthetic Conjugated Oestrogens, A.

Синтетические Коньюгированные Эстрогены, А

Synthetic Conjugated Estrogens, B *(USAN)*

CE-10; Synthetic Conjugated Oestrogens, B.

Синтетические Коньюгированные Эстрогены, В

CAS — 746658-13-9.

Adverse Effects and Precautions

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

Effects on the cardiovascular system. In an early study of *men* with a previous myocardial infarction, treatment with conjugated oestrogens 5 mg daily was stopped because of a higher incidence of subsequent coronary events.[1] Moreover, treatment with the lower 2.5 mg dose was later also stopped because of suggestions of adverse trends including a greater incidence of venous thromboembolism.[2]

For the cardiovascular effects of HRT, including conjugated oestrogens, in women, see p.2073.

1. Coronary Drug Project Research Group. The Coronary Drug Project: initial findings leading to modifications of its research protocol. *JAMA* 1970; **214:** 1303–13.
2. Coronary Drug Project Research Group. The Coronary Drug Project: findings leading to discontinuation of the 2.5-mg/day estrogen group. *JAMA* 1973; **226:** 652–7.

Effects on the nervous system. Reversible chorea has been described in 2 women given conjugated oestrogens with a progestogen as postmenopausal HRT;[1,2] in 1 case the patient had a history of migraine and Sydenham's chorea.[1] Chorea also recurred in a postmenopausal woman with a history of chorea gravidarum when she was given vaginal conjugated oestrogens.[3]

1. Steiger MJ, Quinn NP. Hormone replacement therapy induced chorea. *BMJ* 1991; **302:** 762.
2. Suchowersky O, Muthipeedika J. A case of late-onset chorea. *Nat Clin Pract Neurol* 2005; **1:** 113–16.
3. Caviness JN, Muenter MD. An unusual cause of recurrent chorea. *Mov Disord* 1991; **6:** 355–7.

Hypersensitivity. An anaphylactic reaction after intravenous conjugated oestrogens has been reported.[1]

1. Searcy CJ, *et al.* Anaphylactic reaction to intravenous conjugated estrogens. *Clin Pharm* 1987; **6:** 74–6.

Interactions

See under Hormone Replacement Therapy, p.2076.

Pharmacokinetics

Conjugated oestrogens taken orally are hydrolysed by enzymes present in the intestine that remove the sulfate group and allow absorption of the unconjugated oestrogen. Metabolism occurs primarily in the liver; there is some enterohepatic recycling (see also under Estradiol, p.2098).

Uses and Administration

Conjugated oestrogens have actions and uses similar to those described for estradiol (see p.2098).

When used as menopausal HRT (p.2076) doses of 0.3 to 1.25 mg daily are given orally either cyclically or continuously, with a progestogen either cyclically or continuously in women with a uterus. Doses of 0.3 to 1.25 mg may also be used for the prevention of postmenopausal osteoporosis, but oestrogen therapy is generally reserved for women who are at significant risk and who cannot be given non-hormonal treatment. Topical vaginal therapy may be used specifically for menopausal atrophic vaginitis, atrophic urethritis, and kraurosis vulvae; 0.5 to 2 g of a 0.0625% cream may be used daily for 3 weeks of a 4-week cycle. For women with a uterus, the addition of cyclical progestogen is generally not required during topical vaginal oestrogen therapy. However, the use of a progestogen may be considered, and during long-term therapy these women should be monitored for evidence of endometrial hyperplasia.

When given as replacement therapy on a cyclical basis, oral doses of 1.25 mg daily are used for primary ovarian failure, adjusted according to response. Doses of 300 to 625 micrograms daily are usually given for female hypogonadism, although higher doses were formerly used.

For the palliative treatment of prostatic carcinoma (p.671), an oral dose of 1.25 to 2.5 mg three times daily has been used. A dose of 10 mg three times daily for at least 3 months has been used for palliative treatment of breast carcinoma in men (p.663) and postmenopausal women (p.661).

Abnormal uterine bleeding has been treated acutely by giving 25 mg of conjugated oestrogens by slow intravenous injection, repeated if required after 6 to 12 hours; the intramuscular route has also been used.

Synthetic conjugated oestrogens are derived from plant material, and are not a generic equivalent of Conjugated Estrogens described in USP 31 (see above). Synthetic conjugated estrogens, A, contains a mixture of nine derivatives of estrone, equilin, estradiol, and equilenin. It is used in oral doses of 0.45 to 1.25 mg daily for the relief of vasomotor symptoms associated with the menopause. A dose of 300 micrograms daily may be used for menopausal vulvar and vaginal atrophy, but an alternative topical therapy should be considered if this is the only symptom being treated. Synthetic conjugated estrogens, B, contains a mixture of ten derivatives of estrone, equilin, estradiol, and equilenin. It is used in oral doses of 0.3 to 1.25 mg daily for the relief of vasomotor symptoms associated with the menopause. A dose of 300 micrograms daily may be used for menopausal vulvar and vaginal atrophy, but an alternative topical therapy should be considered if this is the only symptom being treated.

Administration in children. Conjugated oestrogens have been used to reduce final height in girls with constitutional tall stature (see Growth Disorders, under Estradiol, p.2099). They have also been used in children for some haemorrhagic disorders (below).

Haemorrhagic disorders. Case reports and small studies have described the use of high-dose conjugated oestrogens in the management of haemorrhagic disorders associated with renal failure,[1-5] although it is unclear how oestrogens might reduce prolonged bleeding times in these patients.[6] Treatment has been given orally, but an intravenous dose of 600 micrograms/kg given over 30 to 40 minutes, once daily for 5 days, has been reported most often.[6]