Profasi; **UK:** Choragon; Ovitrelle; Pregnyl; **USA:** Chorex†; Choron; Gonic; Novarel; Ovidrel; Pregnyl; Profasi; **Venez.:** Ovidrel; Pregnyl; Profasi†.

Multi-ingredient: **Ger.:** NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; **Mex.:** Gonakor.

Clomifene Citrate *(BANM, rINNM)* ⊗

Chloramiphene Citrate; Citrato de clomifeno; Clomifène, citrate de; Clomifeni citras; Clomiphene Citrate *(USAN)*; Klomifeenisitraatti; Klomifen Sitrat; Klomifencitrat; Klomifén-citrát; Klomifencitrát; Klomifeno citratas; MER-41; MRL-41; NSC-35770. A mixture of the *E* and *Z* isomers of 2-[4-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate.

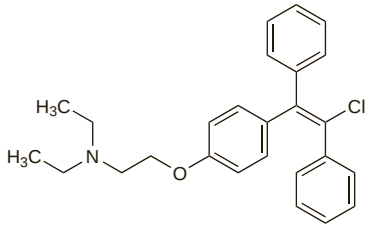
Кломифена Цитрат

$C_{26}H_{28}ClNO,C_6H_8O_7$ = 598.1.

CAS — 911-45-5 (clomifene); 15690-57-0 ((E)-clomifene); 15690-55-8 ((Z)-clomifene); 50-41-9 (clomifene citrate); 7599-79-3 ((E)-clomifene citrate); 7619-53-6 ((Z)-clomifene citrate).

ATC — G03GB02.

ATC Vet — QG03GB02.



(clomifene)

NOTE. Clomifene may be separated into its *Z*- and *E*-isomers, zuclomifene and enclomifene.

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

Ph. Eur. 6.2 (Clomifene Citrate). A white or pale yellow, crystalline powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water; sparingly soluble in alcohol. Protect from light.

USP 31 (Clomiphene Citrate). A white to pale yellow, essentially odourless powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water and in chloroform; sparingly soluble in alcohol; insoluble in ether; freely soluble in methyl alcohol.

Adverse Effects

The incidence and severity of adverse effects of clomifene citrate tend to be related to the dose used. The most commonly reported adverse effects are reversible ovarian enlargement and cyst formation, vasomotor flushes resembling menopausal symptoms, and abdominal or pelvic discomfort or pain, sometimes with nausea or vomiting. Ovarian hyperstimulation syndrome has occurred. Breast tenderness, abnormal uterine bleeding, weight gain, headache, and endometriosis have also been reported. Transient visual disturbances such as spots or flashes, after-images, and blurring of vision may occur, and there have been rare reports of cataracts and optic neuritis. Skin reactions such as allergic rashes and urticaria have occasionally been reported and reversible hair loss has been reported rarely. CNS disturbances have included convulsions, dizziness, lightheadedness, nervous tension, fatigue, vertigo, insomnia, and depression. Abnormalities in liver function tests and jaundice have sometimes been reported.

There is an increased risk of multiple births with clomifene therapy, but rarely more than twins. There is also an increased risk of ectopic pregnancy. Although there have been reports of congenital disorders such as neural tube defects or Down's syndrome in infants born to women treated with clomifene, the role of the drug in the causation of these defects has not been established and the incidence is reported to be similar to that for the general population.

Carcinogenicity. There have been a number of reports suggesting an association between drug therapy to treat infertility by stimulating ovulation and the subsequent development of ovarian cancer.[1-5] Concern has focused in particular on the use of clomifene citrate and gonadotrophins, and a study has reported an increased risk of ovarian cancer in women who had prolonged clomifene therapy (for one year or more) although not in those who received the drug for a shorter period.[6] No association between gonadotrophin therapy and ovarian cancer was noted in this study. The conclusions of this study were only tentative, since the numbers who developed ovarian cancer were small; it has been pointed out that a successfully achieved pregnancy may reduce the risk of some other cancers, and that the risks and benefits of the procedure are not easy to balance.[7] A review[8] of epidemiological and cohort studies concluded that clomifene was not associated with any increase in the risk of ovarian cancer when used for less than 12 cycles, but noted conflicting results, limitations of the data, and the need to control for infertility and nulliparity as risk factors for ovarian cancer. Further cohort[9,10] and case-control[11] studies, and pooled analyses,[12,13] have also found no association between use of clomifene and ovarian cancer.

As a matter of prudence the UK CSM has recommended that clomifene should not normally be used for more than 6 cycles.[14] However, the UK guidelines[15] on the treatment of infertility considered that the limit of 6 cycles related to one course of treatment only. In practice many women required more than one course and it was considered that benefit may be derived from use of up to 12 cycles.

1. Fishel S, Jackson P. Follicular stimulation for high tech pregnancies: are we playing it safe? *BMJ* 1989; **299:** 309–11.
2. Kulkarni R, McGarry JM. Follicular stimulation and ovarian cancer. *BMJ* 1989; **299:** 740.
3. Dietl J. Ovulation and ovarian cancer. *Lancet* 1991; **338:** 445.
4. Willemsen W, *et al.* Ovarian stimulation and granulosa-cell tumour. *Lancet* 1993; **341:** 986–8.
5. Tewari K, *et al.* Fertility drugs and malignant germ-cell tumour of ovary in pregnancy. *Lancet* 1998; **351:** 957–8.
6. Rossing MA, *et al.* Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994; **331:** 77–6.
7. Whittemore AS. The risk of ovarian cancer after treatment for infertility. *N Engl J Med* 1994; **331:** 805–6.
8. Duckitt K, Templeton AA. Cancer in women with infertility. *Curr Opin Obstet Gynecol* 1998; **10:** 199–203.
9. Potashnik G, *et al.* Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. *Fertil Steril* 1999; **71:** 853–9.
10. Brinton LA, *et al.* Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol* 2004; **103:** 1194–1203.
11. Rossing MA, *et al.* A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* 2004; **160:** 1070–8.
12. Ness RB, *et al.* Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002; **155:** 217–24.
13. Kashyap S, *et al.* Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. *Obstet Gynecol* 2004; **103:** 785–94.
14. CSM/MCA. Clomiphene (Clomid, Serophene): possible association with ovarian cancer. *Current Problems* 1995; **21:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)
15. National Collaborating Centre for Women's and Children's Health/National Institute for Clinical Excellence. Fertility: assessment and treatment for people with fertility problems (issued February 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/Fertility_full.pdf (accessed 30/06/08) or http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 30/06/08)

Effects on the CNS. An infertile woman had convulsions when given clomifene citrate;[1] only 5 other cases had been reported since 1963.

1. Rimmington MR, *et al.* Convulsions after clomiphene citrate. *BMJ* 1994; **309:** 512.

Effects on the eyes. As mentioned above, clomifene may cause visual disturbances, which resolve on stopping treatment. However, visual symptoms have persisted in a few cases.[1]

1. Purvin VA. Visual disturbance secondary to clomiphene citrate. *Arch Ophthalmol* 1995; **113:** 482–4.

Effects on the fetus. After reports of neural tube defects in fetuses conceived after ovulation induction, analyses of congenital defect registers and follow-up studies of clomifene use suggested that the drug might possibly be associated with an increase in risk.[1-5] However, subsequent studies reported no increased risk,[6-8] and a pooled analysis[9] of 10 epidemiological studies found no strong evidence to confirm an association. Further studies have also reported no increased risk of neural tube defects[10] or hypospadias in male offspring[11] after exposure to fertility treatment. However, another case-control study[12] did find a potential association between clomifene and neural tube defects, but noted that because of the low baseline prevalence of the malformation, the absolute risk difference would be small. It is not clear whether the underlying infertility itself affects the risk of congenital defects and whether it may confound the calculated risk associated with clomifene.[9]

1. Cornel MC, *et al.* Ovulation induction and neural tube defects. *Lancet* 1989; **i:** 1386.
2. Czeizel A. Ovulation induction and neural tube defects. *Lancet* 1989; **ii:** 167.
3. Cuckle H, Wald N. Ovulation induction and neural tube defects. *Lancet* 1989; **ii:** 1281.
4. Cornel MC, *et al.* Ovulation induction, in-vitro fertilisation, and neural tube defects. *Lancet* 1989; **ii:** 1530.
5. Vollset SE. Ovulation induction and neural tube defects. *Lancet* 1990; **337:** 178.
6. Mills JL, *et al.* Risk of neural tube defects in relation to maternal fertility and fertility drug use. *Lancet* 1990; **336:** 103–4.
7. Rosa F. Ovulation induction and neural tube defects. *Lancet* 1990; **336:** 1327.
8. Werler MM, *et al.* Ovulation induction and risk of neural tube defects. *Lancet* 1994; **344:** 445–6.
9. Greenland S, Ackerman DL. Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. *Fertil Steril* 1995; **64:** 936–41.
10. Whiteman D, *et al.* Reproductive factors, subfertility, and risk of neural tube defects: a case-control study based on the Oxford Record Linkage Study Register. *Am J Epidemiol* 2000; **152:** 823–8.
11. Sørensen HT, *et al.* Use of clomifene during early pregnancy and risk of hypospadias: population based case-control study. *BMJ* 2005; **330:** 126–7.
12. Wu YW, *et al.* Potential association between infertility and spinal neural tube defects in offspring. *Birth Defects Res A Clin Mol Teratol* 2006; **76:** 718–22.

Effects on mental function. Acute psychotic reactions with paranoid tendencies have occurred rarely during clomifene use.[1,2]

1. Siedentopf F, *et al.* Clomiphene citrate as a possible cause of a psychotic reaction during infertility treatment. *Hum Reprod* 1997; **12:** 706–7.
2. Oyffe I, *et al.* Clomiphene-induced psychosis. *Am J Psychiatry* 1997; **154:** 1169–70.

Precautions

Clomifene is contra-indicated in patients with liver disease or a history of liver dysfunction. It should not be used in pregnancy. Clomifene should not be used in women with uterine bleeding that is undiagnosed or caused by hormone-dependent tumours, or in patients with pre-existing mental depression or thrombophlebitis because of the risk of exacerbation. Patients should be warned of the possibility of multiple births.

Clomifene should not be given to women with ovarian cysts, except those with polycystic ovary syndrome, and the lowest doses possible should be used to minimise ovarian enlargement or cyst formation; some patients with polycystic ovary syndrome may have an exaggerated response to usual doses of clomifene. Patients should be instructed to report any abdominal or pelvic pain, distension, or weight gain, as this may indicate the presence or enlargement of ovarian cysts. They should also be evaluated for the presence of ovarian cysts before each cycle of treatment. If abnormal enlargement occurs, clomifene should not be given until the ovaries have returned to pre-treatment size, and subsequent doses should be reduced. Clomifene should be used with caution in patients with uterine fibroids, due to the potential for enlargement of the fibroids.

Treatment should be stopped if visual disturbances develop and the patient warned that this might affect their ability to drive or operate machinery. Long-term cyclic therapy is not recommended, because of the uncertainty regarding increased risk of ovarian cancer: a maximum of 6 cycles of treatment has generally been advised, but see also under Carcinogenicity, above.

Pharmacokinetics

Clomifene citrate is absorbed from the gastrointestinal tract. It is metabolised in the liver and slowly excreted via the bile. Unchanged drug and metabolites are excreted in the faeces. The biological half-life is reported to be 5 days although traces are found in the faeces for up to 6 weeks. Enterohepatic recirculation takes place. The *E*-isomer is reported to be less well absorbed and more rapidly eliminated than the *Z*-isomer.

◊ References.

1. Szutu M, *et al.* Pharmacokinetics of intravenous clomiphene isomers. *Br J Clin Pharmacol* 1989; **27:** 639–40.

Uses and Administration

Clomifene is a nonsteroidal compound that has both oestrogenic and anti-oestrogenic properties, the latter residing principally in the *E*-isomer. Its action in stimulating ovulation is believed to be related to its anti-oestrogenic properties. It stimulates the secretion of pituitary gonadotrophic hormones, probably by blocking the negative feedback effect of oestrogens at receptor sites in the hypothalamus and pituitary.

Clomifene is the most widely used drug in the treatment of anovulatory infertility (p.2080). Therapy with clomifene will not be successful unless the woman, though anovulatory, is capable of ovulation and her partner is fertile. It is ineffective in primary pituitary or

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.

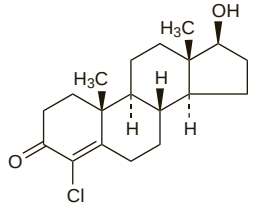
Clostebol Acetate *(BAN, rINNM)* ⊗

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]