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.

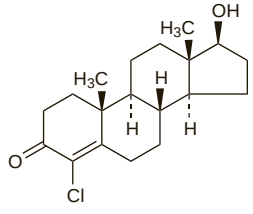
Clostebol Acetate *(BAN, rINNM)* ⊗

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]

Conjugated oestrogens have also been used in various doses in the management of haemorrhagic cystitis (p.2178), particularly that caused by high-dose cyclophosphamide therapy (p.702). The successful use of 25 mg intravenously for 2 consecutive days has been reported,[7] as has a regimen consisting of a 1 mg/kg intravenous dose followed by 5 mg orally for 3 weeks.[8] A report[9] of treatment in 10 patients described the use of oral conjugated oestrogens in doses of 6 to 12 mg daily, usually in three divided doses, for durations of 5 days to 16 weeks.[9] Another report[10] of therapy in 10 children aged between 8 and 19 years described intravenous doses of 12.5 to 50 mg twice daily, often for 2 or 3 days, followed by oral doses ranging from 2.5 mg twice daily to 5 mg four times daily for durations of a few days to about 3 weeks.

Oestrogens have also been used in the treatment of other bleeding disorders (see Estradiol, p.2099).

1. Liu YK, *et al.* Treatment of uraemic bleeding with conjugated oestrogen. *Lancet* 1984; **ii:** 887–90.
2. Livio M, *et al.* Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 1986; **315:** 731–5.
3. Seth S, Geier TM. Use of conjugated estrogens to control gastrointestinal tract bleeding in two patients with chronic renal failure. *Clin Pharm* 1988; **7:** 906–9.
4. Shemin D, *et al.* Oral estrogens decrease bleeding time and improve clinical bleeding in patients with renal failure. *Am J Med* 1990; **89:** 436–40.
5. Heunisch C, *et al.* Conjugated estrogens for the management of gastrointestinal bleeding secondary to uremia of acute renal failure. *Pharmacotherapy* 1998; **18:** 210–7.
6. Hedges SJ, *et al.* Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007; **3:** 138–53.
7. Kopterides P, *et al.* Cyclophosphamide-induced hemorrhagic cystitis successfully treated with conjugated estrogens. *Am J Hematol* 2005; **80:** 166–7.
8. Rodriguez Luna JM, *et al.* Control of massive hematuria in idiopathic hemorrhagic cystitis after administration of conjugated estrogen. *J Urol (Baltimore)* 1992; **148:** 1524–5.
9. Ordemann R, *et al.* Encouraging results in the treatment of haemorrhagic cystitis with estrogen–report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; **25:** 981–5.
10. Heath JA, *et al.* Estrogen as treatment of hemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation. *Bone Marrow Transplant* 2006; **37:** 523–6.

Preparations

USP 31: Conjugated Estrogens Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Belestar; Livomarin; Premarin; ***Austral.:*** Premarin; ***Austria:*** Conjugen†; Oestro-Feminal†; Premarin; ***Belg.:*** Premarin†; ***Braz.:*** Estrogenon; Estroplus; Gestrocon; Menoprin; Menosedan†; Prem; Premarin; Repogen; ***Canad.:*** CES; Congest; Premarin; ***Chile:*** Climatrol E; Conpremin; Estrarona; Profemina; ***Cz.:*** Oestrofeminal†; Premarin†; Presomen†; ***Denm.:*** Premarin†; ***Fin.:*** Premarin†; ***Fr.:*** Premarin†; ***Ger.:*** Climarest†; Climopax mono; Femavit†; Oestrofeminal†; Presomen; Transannon†; ***Gr.:*** Premarin; ***Hong Kong:*** Equin; Premarin; ***Hung.:*** Premarin†; ***India:*** Espauz; Estrin; Premarin; ***Irl.:*** Premarin; ***Israel:*** Premaril†; Prevagin-Premaril†; ***Ital.:*** Emopremarin†; Premarin†; ***Malaysia:*** Premarin; ***Mex.:*** Equifan; Fahifem; Neradin; Premarin; Six Din; Sultrona; Terapova; ***Neth.:*** Dagynil; Premarin†; PremarinLite†; ***NZ:*** Premarin; ***Philipp.:*** Menpoz; Premarin; ***S.Afr.:*** Premarin; ***Singapore:*** Equin; Premarin; ***Spain:*** Equin; Longaplex; Premarin†; ***Swed.:*** Premarina†; ***Switz.:*** Premarin; Transannon†; ***Thai.:*** Estromon; Premarin; ***Turk.:*** Premarin; ***UK:*** Premarin; ***USA:*** Cenestin; Enjuvia; Premarin; ***Venez.:*** Biostrogen; Climatrol E; Menostat; Premarin.

Multi-ingredient: ***Arg.:*** Periofem Ciclico†; Periofem Continuo†; Premelle Ciclico†; Premelle Continuo†; ***Austral.:*** Menoprem†; Premia; Premia Continuous; Premia Low†; Provelle†; ***Austria:*** Perennia; Premarin compositum†; Premarin Plus; Sequennia; ***Belg.:*** Premelle Cycle†; Premelle†; Premplus†; ***Braz.:*** Menosedan Ciclo†; Menosedan Fase†; Menosedan MPA†; Menotensil; Premarin MPA†; Premelle; Premelle Ciclo; Prempro Bifasico; Prempro Monofasico; Repogen Ciclo; Repogen Conti; Selecta; ***Canad.:*** Premplus; ***Chile:*** Climatrol Continuo; Climatrol HT; Climatrol HT Continuo; Conpremin Pak; Conpremin Pak Plus; Novafac; Novafac 30; Novafac CC; Prempak†; Profemina CC†; Profemina MP; ***Cz.:*** Cyclo-Premella†; Premella†; Presomen Compositum†; ***Ger.:*** Climopax; Climopax Cyclo; Presomen Compositum; ***Gr.:*** Premelle; Premelle Cycle; ***Hong Kong:*** Premelle; Premelle Cycle; Prempak†; ***Hung.:*** Cyclo-Premella†; Premella†; ***Irl.:*** Premique; Premique Cycle; Prempak-C; ***Israel:*** Premaril MP†; Premaril Plus MP†; ***Ital.:*** Premelle Combinato; Premelle S†; Premelle Sequenziale†; Prempak†; ***Malaysia:*** Plentiva Cycle 5†; Plentiva†; Premelle; Prempak†; ***Mex.:*** Premelle; ***Neth.:*** Premarin Plus†; Premelle Cycle†; Premelle†; PremelleLite†; Prempak-C†; ***NZ:*** Menoprem†; Premia Continuous; Premia†; Prempak-C†; ***Philipp.:*** Premelle; Premelle Cycle; ***Port.:*** Premarin Plus†; Premelle Cycle†; Premelle†; ***S.Afr.:*** Premelle; Premelle Cycle; Prempak N; ***Singapore:*** Premelle Cycle†; Premelle†; Prempak-C; ***Spain:*** Premelle; Premelle Ciclico; ***Swed.:*** Premelle Sekvens†; Premelle†; ***Switz.:*** Cyclo-Premella ST; Premarin Plus†; Premella; Premia†; ***Thai.:*** Premelle Cycle†; Premelle†; ***Turk.:*** Premelle; Premelle Cycle; ***UK:*** Premique; Premique Cycle; Prempak-C; ***USA:*** Premphase; Prempro; ***Venez.:*** Climatrol HT Ciclico; Climatrol HT Continuo; Cyclogesterin†; Premelle Ciclico†; Premelle Continuo; Premelle Plus Continuo†.

Cyclofenil *(BAN, rINN)* ⊗

Ciclofenilo; Cyclofénil; Cyclofenilum; Cyklofenil; F-6066; H-3452; ICI-48213; Siklofenil; Syklofeniili. 4,4′-(Cyclohexylidenemethylene)bis(phenyl acetate).

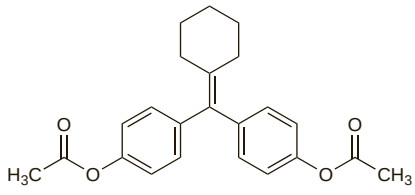
Циклофенил

$C_{23}H_{24}O_4$ = 364.4.

CAS — 2624-43-3.

ATC — G03GB01.

ATC Vet — QG03GB01.



Profile

Cyclofenil is a nonsteroidal anti-oestrogen that has been used in the treatment of menstrual disturbances and anovulatory infertility due to hypothalamic-pituitary dysfunction.

It has been given orally in doses of 200 mg three times daily for 5 days, in a cyclical regimen for 3 or 4 cycles. It has also been given for menopausal symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Menopax; ***Ital.:*** Neoclym; ***Mex.:*** Fertodur†; ***Turk.:*** Fertodur.

Cyproterone Acetate *(BANM, USAN, rINNM)*

Acetato de ciproterona; Ciproteron-acetát; Ciproterono acetatas; Cyproteronacetat; Cyproteron-acetát; Cyprotérone, acétate de; Cyproteroni acetas; NSC-81430; SH-714; SH-881 (cyproterone); Siproteron Asetat; Syproteroniasetaatti. 6-Chloro-1β,2β-dihydro-17α-hydroxy-3′*H*-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione acetate.

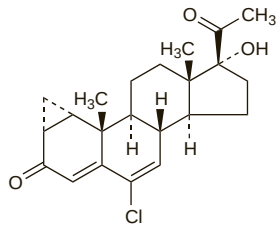
Ципротерона Ацетат

$C_{24}H_{29}ClO_4$ = 416.9.

CAS — 2098-66-0 (cyproterone); 427-51-0 (cyproterone acetate).

ATC — G03HA01.

ATC Vet — QG03HA01.



(cyproterone)

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

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

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

Ph. Eur. 6.2 (Cyproterone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone; very soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Adverse Effects

When given to men cyproterone reduces libido, inhibits spermatogenesis, reduces the volume of ejaculate, and causes infertility. There may be azoospermia after 8 weeks and slight atrophy of the seminiferous tubules, but these changes are slowly reversible and spermatogenesis usually recovers to pre-treatment levels about 3 to 5 months after stopping cyproterone. Abnormal spermatozoa may be produced. Gynaecomastia is common and permanent enlargement of the mammary glands may occur; galactorrhoea and benign nodules have been reported rarely. Fatigue and weakness are common and depressive mood changes can occur occasionally. Patients may experience weight changes, alterations in hair pattern, dry skin, and rarely rashes or hypersensitivity. Shortness of breath may occur, and anaemia and osteoporosis have been reported rarely. Liver function tests may be altered; there have also been reports of hepatitis, jaundice, and hepatic failure, sometimes fatal, developing usually after several months of high-dose cyproterone therapy, but an association with liver cancer is uncertain.

When low-dose cyproterone is given with ethinylestradiol to women, adverse effects associated with combined oral contraceptives (see p.2059) may occur.

Carcinogenicity. See Effects on the Liver, below.

Effects on the cardiovascular system. Combined oral contraceptives are associated with a small increased risk of cardiovascular disease (see p.2062). A case-control study suggested that the risk of venous thromboembolism may be further increased for women taking combined contraceptives containing cyproterone compared with levonorgestrel.[1] A review by the authorities in New Zealand considered the risk to be at least as great as with third-generation oral contraceptives,[2] a conclusion further supported by a study in that country of the contraceptives used by women discharged from hospital with a diagnosis of deep-vein thrombosis or pulmonary embolism.[3] In 2002, the UK CSM[4] warned that preparations containing cyproterone and ethinylestradiol should not be used solely for contraception, but for treatment of severe acne that had not responded to oral antibacterials, or for moderately severe hirsutism, and that they should be withdrawn 3 or 4 cycles after the treated condition has completely resolved. However, others[5,6] have questioned some study results, concluding that preparations containing cyproterone are not associated with a risk in excess of that associated with conventional combined oral contraceptives including those containing levonorgestrel. Some[7] have also called for the removal of the CSM recommendation to limit the duration of therapy, particularly as acne and hirsutism frequently recur after stopping cyproterone therapy. In 2008, the CHM (formerly the CSM) reconfirmed its 2002 advice on the use of cyproterone with ethinylestradiol.[8] However, it added that for women with severe hyperandrogenism, in whom symptoms usually recur when treatment is stopped, therapy could be continued with regular specialist review until the symptoms were judged unlikely to recur. It was also recommended that, for all women, treatment can be restarted at any time if acne or hirsutism recurs after stopping therapy.

The study of any association may be confounded by the adverse cardiovascular risk associated with polycystic ovary disease, an underlying condition in many women given cyproterone with ethinylestradiol to manage acne and hirsutism.[6]

1. Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. *Lancet* 2001; **358:** 1427–9.
2. Savage R. New Zealand Medicines and Medical Devices Safety Authority. Venous thromboembolism with Diane 35 and Estelle 35 (issued March 2002). Available at: http://www.medsafe.govt.nz/Profs/PUarticles/VTEwithCPA.htm (accessed 27/06/08)
3. Heuser P, *et al.* Specific oral contraceptive use and venous thromboembolism resulting in hospital admission. *N Z Med J* 2004; **117:** U1176. Available at: http://www.nzma.org.nz/journal/117-1206/1176/content.pdf (accessed 27/06/08)
4. CSM/MCA. Cyproterone acetate (Dianette): risk of venous thromboembolism (VTE). *Current Problems* 2002; **28:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 27/06/08)
5. Spitzer WO. Cyproterone acetate with ethinylestradiol as a risk factor for venous thromboembolism: an epidemiological evaluation. *J Obstet Gynaecol Can* 2003; **25:** 1011–18.
6. Seaman HE, *et al.* Venous thromboembolism associated with cyproterone acetate in combination with ethinyloestradiol (Dianette): observational studies using the UK General Practice Research Database. *Pharmacoepidemiol Drug Safety* 2004; **13:** 427–36.
7. Franks S, *et al.* Cyproterone acetate/ethinyl estradiol for acne and hirsutism: time to revise prescribing policy. *Hum Reprod* 2008; **23:** 231–2.
8. MHRA/CHM. Cyproterone acetate with ethinylestradiol (co-cyprindiol): recommended duration of use. *Drug Safety Update* 2008; **1** (9): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=LatestReleased (accessed 22/08/08)

Effects on the eyes. Bilateral optic atrophy in an elderly male patient was thought to be associated with cyproterone.[1] The authors could find no other cases from the published literature or the manufacturers' records. Central retinal vein occlusion occurred in a 28-year-old woman given cyproterone for the treatment of hair loss.[2]

1. Markus H, *et al.* Visual loss and optic atrophy associated with cyproterone acetate. *BMJ* 1992; **305:** 159.
2. Zaoui M, *et al.* Occlusion de la veine centrale de la rétine sous anti-androgènes. *J Fr Ophtalmol* 2000; **23:** 42–4.

Effects on the liver. There have been numerous reports of hepatic reactions associated with cyproterone acetate. In February 1995, the UK CSM noted that it had received 96 reports of reactions including hepatitis, cholestatic jaundice, and hepatic failure, following cyproterone treatment;[1] 33 cases had led to fatalities. Nearly all cases (91 of 96) were in elderly men typically receiving high doses (300 mg daily) for prostatic cancer, and toxicity usually developed after several months of treatment. In view of this it was recommended that the use of cyproterone acetate in prostatic cancer be restricted to short courses for the testosterone flare associated with the commencement of gonadore-