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).

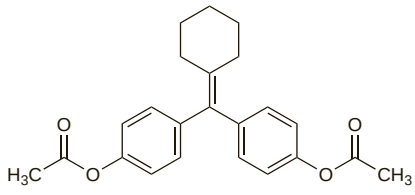
Циклофенил

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

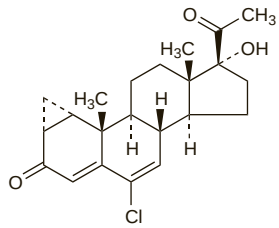
Ципротерона Ацетат

$C_{24}H_{29}ClO_4$ = 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-