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†.

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## Cyclofenil *(BAN, rINN)* ⊗

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

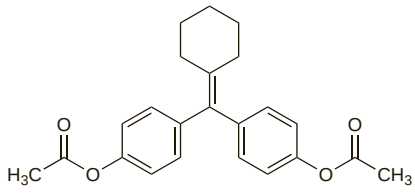
Циклофенил

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

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## 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.

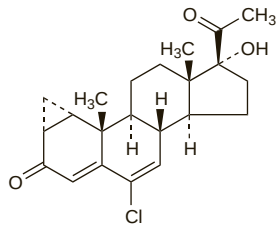
Ципротерона Ацетат

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

lin analogue therapy, or for hot flushes after surgical or chemical castration, or for patients unresponsive to, or intolerant of, other treatments. A retrospective analysis[2] of data from 105 patients with advanced prostate cancer, who had received cyproterone acetate 150 mg daily, found mild to moderate hepatotoxicity in 6 patients and severe toxicity in 4. There was a higher occurrence of hepatotoxicity (19 cases out of 124 patients) in a similar group that had been given flutamide. Fourteen published case reports have also been briefly reviewed.[3] Patients with chronic viral hepatitis might be at higher risk of developing hepatotoxicity from cyproterone therapy.[4]

Although there is little doubt of the risk of hepatotoxicity, suggestions of an association between cyproterone therapy and the development of liver cancer remain contentious. There are individual reports of hepatocellular carcinoma developing in patients receiving cyproterone,[5,6] and some evidence *in vitro* of the formation of DNA adducts in exposed hepatocytes,[7] but there does not seem to be clinical evidence to support any association between use of cyproterone acetate and the development of liver tumours.[7,8]


1. CSM/MCA. Hepatic reactions with cyproterone acetate (Cyprostat, Androcur). *Current Problems* 1995; **21:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 27/06/08)
2. Lin ADY, *et al.* Antiandrogen-associated hepatotoxicity in the management of advanced prostate cancer. *J Chin Med Assoc* 2003; **66:** 735–40.
3. Savidou I, *et al.* Hepatotoxicity induced by cyproterone acetate: a report of three cases. *World J Gastroenterol* 2006; **12:** 7551–5.
4. Pu Y-S, *et al.* Antiandrogen hepatotoxicity in patients with chronic viral hepatitis. *Eur Urol* 1999; **36:** 293–7.
5. Watanabe S, *et al.* Three cases of hepatocellular carcinoma among cyproterone users. *Lancet* 1994; **344:** 1567–8.
6. Rüdiger T, *et al.* Hepatocellular carcinoma after treatment with cyproterone acetate combined with ethinyloestradiol. *Lancet* 1995; **345:** 452–3.
7. Lewis S. Warning on cyproterone. *Lancet* 1995; **345:** 247.
8. Rabe T, *et al.* Liver tumours in women on oral contraceptives. *Lancet* 1994; **344:** 1568–9.


## Precautions

When used for hypersexuality, cyproterone is contra-indicated in men with liver diseases or malignant or wasting diseases. In addition, it should not be given to men with severe chronic depression, severe diabetes with vascular changes, sickle-cell anaemia, or to those with a history of thromboembolic disorders. It may delay bone maturation and testicular development and so should not be given to immature youths. When used for prostate cancer, there are no absolute contra-indications to the use of cyproterone, but the above conditions should prompt cautious consideration of the risks and benefits.

In men treated with cyproterone, liver function should be monitored before starting, and regularly during, treatment, and whenever any symptoms or signs suggestive of hepatotoxicity occur. If cyproterone-induced hepatotoxicity occurs, treatment should be withdrawn. In men with prostate cancer, it may be advisable to limit the duration of treatment (see Effects on the Liver, above). Men with diabetes require careful monitoring of diabetic control. Since anaemia has been seen, regular blood counts are recommended before and during treatment. Adrenocortical suppression has been reported and function should be monitored regularly during treatment. Patients should be advised that fatigue and weakness are common and may interfere with driving and the operation of machinery.

When cyproterone is given with ethinylestradiol to women the precautions for combined oral contraceptives (see p.2065) should be observed.

**Pregnancy.** Use of cyproterone during pregnancy might carry a risk of feminisation of a male fetus. However, there are a few case reports of healthy male infants born to mothers who had inadvertently taken a combination of cyproterone acetate and ethinylestradiol during the early stages of pregnancy,[1,2] and of a male fetus that was found to have no malformations after abortion was induced.[3] For further information on oral contraceptive use in pregnancy, see p.2067.


1. Statham BN, *et al.* Conception during 'Diane' therapy—a successful outcome. *Br J Dermatol* 1985; **113:** 374.
2. Bye P. Comments on 'conception during "Diane" therapy—a successful outcome'. *Br J Dermatol* 1986; **114:** 516.
3. Bergh T, Bakos O. Exposure to antiandrogen during pregnancy: case report. *BMJ* 1987; **294:** 677–8.


## Interactions

UK licensed product information states that alcohol may reduce the effectiveness of cyproterone acetate as it is ineffective in chronic alcoholics. Dosage requirements of oral antidiabetics and insulin may be altered because of cyproterone's effects on carbohydrate metabolism.

When given with ethinylestradiol to women, interactions similar to those for combined oral contraceptives (see p.2067) might be anticipated.

## Pharmacokinetics

Cyproterone acetate is slowly absorbed from the gastrointestinal tract with peak plasma concentrations being achieved in about 3 hours. It is about 96% bound to plasma proteins, mainly albumin. The terminal elimination half-life is about 43 hours. Cyproterone is metabolised by various pathways including hydroxylation and conjugation; about 35% of a dose is excreted in urine, the remainder being excreted in the bile. The principal metabolite, 15β-hydroxycyproterone, has anti-androgenic activity.

**The elderly.** In a study[1] of healthy men, a decrease in hepatic clearance of cyproterone acetate was found in elderly men and thought to be due to an age-related reduction in liver volume.


1. Kuhnz W, *et al.* Investigation into the age-dependence of the pharmacokinetics of cyproterone acetate in healthy male volunteers. *Eur J Clin Pharmacol* 1997; **53:** 75–80.


## Uses and Administration

Cyproterone acetate is a progestogen (see Progesterone, p.2126) with anti-androgenic properties.

It is used for the **control of libido** in severe hypersexuality or sexual deviation in men (see Disturbed Behaviour, p.954). The usual oral dose is 50 mg twice daily after meals.

It is also used for the palliative treatment of **prostatic carcinoma** (p.671), to control disease flare or hot flushes associated with gonadorelin analogue therapy, and to control hot flushes associated with orchidectomy. In palliative treatment where gonadorelin analogues or surgery are contra-indicated, not tolerated, or where oral therapy is preferred, doses of 200 to 300 mg daily are given in 2 or 3 divided doses after meals. The usual initial dose for disease flare is 300 mg daily in 2 or 3 divided doses after meals, which may be reduced to 200 mg daily if the higher dose is not tolerated. For the treatment of hot flushes, a dose of 50 mg daily is used; this may be increased up to 150 mg daily in 3 divided doses if necessary.

Cyproterone acetate may be used with ethinylestradiol in women for the control of **acne** and **hirsutism** (see below). The usual oral doses are 2 mg of cyproterone acetate with 35 micrograms of ethinylestradiol given daily for 21 days of each menstrual cycle; the first treatment course is started on the first day of the menstrual cycle and each subsequent course is started after 7 tablet-free days have followed the preceding course. This regimen also provides contraception, and patients relying on this effect should be given the same advice regarding missed doses and reduced efficacy due to vomiting and diarrhoea as that given for combined oral contraceptives (see p.2069). Treatment should be withdrawn 3 or 4 cycles after the androgen-dependent condition has completely resolved, but repeat courses may be given if it recurs.

Cyproterone acetate has also been given by depot intramuscular injection. A dose of 300 mg given once every 10 to 14 days has been used to control libido; once a satisfactory effect has been obtained, the dose may be reduced by gradually increasing the interval between injections until a stable maintenance dose is reached. In palliative therapy of prostatic carcinoma, 300 mg may be given once every 2 weeks after orchidectomy, or once weekly without orchidectomy.

Dose-related hepatotoxicity has occurred with cyproterone, particularly in men treated for prostate cancer (see Effects on the Liver and Precautions, above).

**Acne.** Cyproterone acetate may be used in the management of acne (p.1577), generally in women with signs of hyperandrogenism. An oral combination of cyproterone acetate 2 mg with ethinylestradiol 35 micrograms, which also provides contraception, is often used in women whose condition is moderately severe, and may be considered in women with mild acne who wish to use hormonal contraception. In more severe disease, higher doses of cyproterone may be added to this low-dose regimen; examples include giving cyproterone acetate 50 mg daily for 10 or 21 days of each cycle.[1] A systematic review[2] considered that a combination of ethinylestradiol with low-dose cyproterone acetate was more effective in the treatment of acne than combined oral contraceptives containing levonorgestrel, but noted that this was based on limited evidence.


1. Beylot C, *et al.* Oral contraceptives and cyproterone acetate in female acne treatment. *Dermatology* 1998; **196:** 148–52.
2. Arowojolu AO, *et al.* Combined oral contraceptive pills for treatment of acne. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 27/06/08).


**Alopecia.** Cyproterone acetate has been tried in the treatment of female-pattern alopecia (p.1577). In premenopausal women, oral doses of 50 or 100 mg daily have usually been given in sequential regimens with an oestrogen or combined oral contraceptive; continuous treatment using 50 mg daily has been given to postmenopausal women. It has generally been considered that women with other signs of hyperandrogenism, such as acne and seborrhoea, as well as hair loss are most likely to benefit from cyproterone but results from small studies have been mixed.[1-3]


1. Vexiau P, *et al.* Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol* 2002; **146:** 992–9.
2. Carmina E, Lobo RA. Treatment of hyperandrogenic alopecia in women. *Fertil Steril* 2003; **79:** 91–5.
3. Sinclair R, *et al.* Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol* 2005; **152:** 466–73.


**Gender reassignment.** Cyproterone acetate is used for its anti-androgenic effects in male-to-female transsexuals.[1,2] An oral dose of 50 mg twice daily is usually given with an oestrogen (see Estradiol, p.2099).


1. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
2. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.


**Hidradenitis suppurativa.** Beneficial responses to cyproterone acetate with ethinylestradiol have been seen[1-3] in women with hidradenitis suppurativa, an androgen-dependent disorder of the skin and hair in the pubic and axillary regions.


1. Mortimer PS, *et al.* A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol* 1986; **115:** 263–8.
2. Sawers RS, *et al.* Control of hidradenitis suppurativa in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy. *Br J Dermatol* 1986; **115:** 269–74.
3. Mortimer PS, *et al.* Mediation of hidradenitis suppurativa by androgens. *BMJ* 1986; **292:** 961.


**Hirsutism.** Hirsutism is an abnormal growth in females of coarse pigmented terminal hair in an adult male pattern, and is one of the clinical expressions of hyperandrogenism. Most women with hirsutism have increased concentrations of circulating androgens from the ovaries associated with polycystic ovary syndrome (p.2080). In rare cases, the adrenal gland is the primary source of increased androgens, for example, in congenital adrenal hyperplasia (p.1502). In a few cases, severe hirsutism is associated with frank virilisation due to massively increased circulating androgen concentrations from an androgen-secreting tumour. Hirsutism is an adverse effect of androgenic progestogens, such as norgestrel, used in hormonal contraceptives and HRT. Androgens and anabolic steroids may also cause hirsutism in females.

**Treatment** for hirsutism uses topical cosmetic treatments such as bleaching, shaving, plucking, electrolysis, and laser hair removal, and in the mildest cases this may be all that is required. However, such mechanical means of treatment are more usually combined with drug therapy to prevent further conversion of vellus to terminal hair, and to slow the regrowth of terminal hair, which may become lighter and softer. Because the growth cycle of hair is long, a response to therapy may not be seen for 6 to 12 months.[1-3]

Combined *hormonal contraceptives* containing non-androgenic progestogens are widely used for hirsutism but their effects are generally limited.[1-3] The mainstay of oral drug therapy for hirsutism is an anti-androgen, the most commonly used being the steroidal anti-androgens *cyproterone acetate* and *spironolactone*. To increase efficacy (by suppressing ovarian androgen production) and minimise the chance of conception (because of the risk of feminisation of a male fetus), cyclical ethinylestradiol is commonly used with cyproterone acetate. Combined non-androgenic hormonal contraceptives are commonly used with spironolactone, which has no progestogenic activity. Cyproterone acetate may be used in a low-dose combined preparation containing cyproterone acetate 2 mg with ethinylestradiol 35 micrograms.[2-4] In more severe hirsutism, the two drugs may be prescribed separately in a 'reversed sequential regimen'. High-dose regimens[2] have used cyproterone acetate 100 mg daily given on days 5 to 14 of the menstrual cycle with ethinylestradiol 50 micrograms on days 5 to 24. However, lower doses are also effective, with fewer adverse effects; such regimens include[4] cyproterone acetate 50 mg (days 5 to 15) with ethinylestradiol 20 micrograms (days 5 to 25), or cyproterone acetate 12.5 mg (days 5 to 15) with

ethinylestradiol 10 to 20 micrograms (days 5 to 25). Alternatively,[2] cyproterone acetate 25 to 50 mg daily may be added to the first 10 days of any low-dose combined oral contraceptive. When a satisfactory response has been achieved, the cyproterone dosage is gradually reduced, and eventually the low-dose combination preparation may be sufficient.

In some countries spironolactone is the drug of choice for the treatment of hirsutism, particularly if there is associated obesity and hypertension; doses of 100 to 200 mg daily are generally used.[1,2,4] Despite its wide use, however, evidence of benefit is considered scanty.[5] *Flutamide*, *finasteride*, and *leuprorelin* have also been shown to be effective, although some consider finasteride to be less active.[4] The condition has also been reported to respond to *ketoconazole*. *Eflornithine* is used topically for the reduction of facial hair.[1,3,4] It is thought to slow hair growth by the inhibition of ornithine decarboxylase in hair follicles.

Corticosteroids can suppress adrenal androgen production, but results with *dexamethasone* have been disappointing and the addition of an anti-androgen is usually needed.[4] Corticosteroids may have a limited role in managing hirsutism associated with congenital adrenal hyperplasia.[1,2]


1. Rosenfield RL. Hirsutism. *N Engl J Med* 2005; **353:** 2578–88.
2. Claman P, *et al.* Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines no. 110, January 2002: Hirsutism: evaluation and treatment. *J Obstet Gynaecol Can* 2002; **24:** 62–7. Also available at: http://www.sogc.org/guidelines/public/110E-CPG-January2002.pdf (accessed 27/06/08)
3. Moghetti P, Toscano V. Treatment of hirsutism and acne in hyperandrogenism. *Best Pract Res Clin Endocrinol Metab* 2006; **20:** 221–34.
4. Carmina E. A risk-benefit assessment of pharmacological therapies for hirsutism. *Drug Safety* 2001; **24:** 267–76.
5. Farquhar C, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 27/06/08).


**Precocious puberty.** Although cyproterone acetate has been used for the treatment of central precocious puberty (p.2081), it has generally been superseded and is now given in a short course to prevent the initial stimulatory effect of gonadorelin analogue therapy. The use of an oral dose of cyproterone acetate 50 mg twice daily, given from 3 weeks before to 2 weeks after starting the gonadorelin analogue, has been reported.[1] Menstrual-like bleeding may occur in girls after stopping cyproterone, depending on the degree of precocity. Gonadorelin analogue therapy does not control adrenal production of sex hormones, which, if overactive, can stimulate adrenarche and advancement of bone age; cyproterone acetate in usual doses of 10 to 20 mg twice daily has been used to treat this.[1]

Cyproterone acetate may sometimes be used to suppress sexual maturation in the management of peripheral forms of precocious puberty. Although it is not licensed for this, the *BNFC* includes an initial oral dose of 25 mg twice daily, adjusted according to response.


1. Laron Z, Kauli R. Experience with cyproterone acetate in the treatment of precocious puberty. *J Pediatr Endocrinol Metab* 2000; **13** (suppl): 805–10.


## Preparations

***BP 2008:*** Cyproterone Tablets.

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Androcur; Androstat; Asisdun†; Asoteron; Ceprater; Ciclamil; Ciprofarma; Ciproplex; CPD†; Kebirterona; Omnigeriat; Purflx; Rubidox†; ***Austral.:*** Androcur; Cyprohexal; Cyprone; Cyprostat; Procur; ***Austria:*** Androdiane; Androcur; Curandron; ***Belg.:*** Androcur; Cyproplex; ***Braz.:*** Andelux; Androcur; Androneo; Androsteron; Bioterona†; Cetoteron; Ciprostat; ***Canad.:*** Alti-CPA†; Androcur; ***Chile:*** Ciproviron†; ***Cz.:*** Androcur; Cyproplex; Minerva; ***Denm.:*** Androcur; ***Fin.:*** Androcur; ***Fr.:*** Androcur; Kaliale; ***Ger.:*** Androcur; Virilit; ***Gr.:*** Androcur; ***Hong Kong:*** Androcur; ***Hung.:*** Androcur; ***Indon.:*** Androcur; ***Irl.:*** Androcur; ***Israel:*** Androcur; Armocur†; Cypron; ***Ital.:*** Androcur; ***Malaysia:*** Androcur; Cyproplex; ***Mex.:*** Androcur; Neoproxil; ***Neth.:*** Androcur; Curandron; ***Norw.:*** Androcur; ***NZ:*** Androcur; Procur; Siterone; ***Philipp.:*** Androcur; ***Pol.:*** Androcur; ***Port.:*** Androcur; ***Rus.:*** Androcur (Андрокур); ***S.Afr.:*** Androcur; Cyproplex; ***Singapore:*** Androcur; ***Spain:*** Androcur; ***Swed.:*** Androcur; Diane; ***Switz.:*** Androcur; Elleacnelle; ***Thai.:*** Androcur; ***Turk.:*** Androcur; ***UK:*** Androcur; Cyprostat; ***Venez.:*** Androcur; Asoteron.

**Multi-ingredient:** ***Arg.:*** Avancel; Biofem 35; Climene; Diane; Mileva; ***Austral.:*** Brenda-35 ED; Climen; Diane; Estelle; Juliet†; ***Austria:*** Bellgyn; Climen; Dialuna; Diane; Femogyn; Midane; Minerva; Sterigynon; Xylia; ***Belg.:*** Claudia; Climen; Co-Cyproterone; Cyprodiol; Daphne; Diane; Docyproestra; Gratiella; Merckelisa; Ratiopharmeva; ***Braz.:*** Artemidis; Ciprane; Climene; Diane; Elamax; Ferane 35; Repopil; Selene; Tess; ***Canad.:*** Diane; ***Chile:*** Anuar; Climene; Diane; Dixi-35; Drina; Evilin; Lady-Ten 35; ***Cz.:*** Chloe; Climen; Diane; Vreya; ***Denm.:*** Climen; Diane; Dianova; Feminil; ***Fin.:*** Cypretyl; Diane; Femilar; ***Fr.:*** Climene; Diane; Evepar; Holgyeme; Lumalia; Minerva; ***Ger.:*** Attempta; Bella; Clevia; Climen; Cyproderm; Cypronette; Diane; Ergalea; Juliette; ***Gr.:*** Gynofen 35; ***Hong Kong:*** Climen 28; Diane; ***Hung.:*** Climen; Cypromix; Diane; Minerva; ***India:*** Diane; Ginette; ***Indon.:*** Climen 28; Diane; ***Irl.:*** Dianette; ***Israel:*** Diane; Estelle; ***Ital.:*** Climen; Diane; Pausene; Visofid; ***Malaysia:*** Climen; Diane; Estelle; ***Mex.:*** Climene; Diane; Eunice 35-ED; Mileva; ***Neth.:*** Climene; Diane; ***Norw.:*** Climen†; Diane; ***NZ:*** Diane; Estelle; ***Philipp.:*** Althea; Climen 28; Diane; ***Pol.:*** Climen; Cyprest; Diane; ***Port.:*** Climen; Diane; ***Rus.:*** Climen (Климен); Diane (Диане); ***S.Afr.:*** Climen; Diane; Diva; Ginette; Minerva; ***Singapore:*** Climen; Diane; Estelle; ***Spain:*** Climen; Clisin†; Diane; ***Switz.:*** Climen; Cyprestra; Diane; Feminac; Minerva; ***Thai.:*** Climen; Diane; Helen†; Lady-35; Manoane; Preme†; Sucee; ***Turk.:*** Climen; Diane; ***UK:*** Acnocin; Cicafem; Clairette; Dianette; Diva; ***Venez.:*** Climene; Diane; Dixi.

# Danazol *(BAN, USAN, pINN)* ⊗

Danatsoli; Danazolum; Win-17757. 17α-Pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17β-ol.

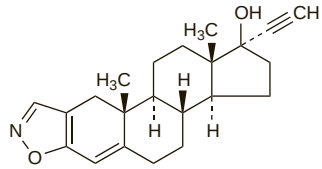
Даназол

$C_{22}H_{27}NO_2$ = 337.5.

*CAS — 17230-88-5.*

*ATC — G03XA01.*

*ATC Vet — QG03XA01.*




**Pharmacopoeias.** In *Chin.* and *US*.

**USP 31** (Danazol). A white to pale yellow crystalline powder. Practically insoluble or insoluble in water and in petroleum spirit; sparingly soluble in alcohol and in benzene; soluble in acetone; freely soluble in chloroform; slightly soluble in ether. Store in airtight containers. Protect from light.

## Adverse Effects

Adverse effects of danazol that reflect inhibition of the pituitary-ovarian axis include menstrual disturbances and amenorrhoea (occasionally persistent), hot flushes, sweating, reduction in breast size, changes in libido, vaginal dryness and irritation, emotional lability, and nervousness.

Adverse effects attributable to androgenic activity include acne, oily skin or hair, mild hirsutism, oedema, weight gain, deepening of the voice, androgenic alopecia, and rarely clitoral hypertrophy. Testicular atrophy and a reduction in spermatogenesis may occur.

Other adverse effects include gastrointestinal disturbances, increased or decreased blood cell counts, thrombotic events, headache, backache, dizziness, tremor, depression, fatigue, sleep disorders, muscle spasm or cramp, skin rash, hyperglucagonaemia, abnormal glucose tolerance, decreased serum high-density-lipoprotein cholesterol, increased serum low-density-lipoprotein cholesterol, and elevation of liver-function test values and rarely cholestatic jaundice. Some patients may experience palpitations, tachycardia, and hypertension. Benign intracranial hypertension and visual disturbances have occurred.

**Effects on carbohydrate metabolism.** Diabetes mellitus developed in a patient given danazol 400 mg twice daily for endometriosis.[1] The diabetes developed 8 weeks after starting danazol therapy and resolved completely after the drug was stopped.


1. Seifer DB, *et al.* Insulin-dependent diabetes mellitus associated with danazol. *Am J Obstet Gynecol* 1990; **162:** 474–5.


**Effects on the liver.** As with other 17α-alkylated steroids (see p.2130), hepatic adverse effects have been associated with danazol, including hepatitis[1] and cholestasis.[2,3] Hepatic adenoma has occurred after long-term danazol use.[4-7] Adenomas are often removed surgically because of the risks of haemorrhage and malignant transformation, but regression over 18 months and 2 years after stopping danazol has been described in 2 patients.[6] There have also been rare reports of focal nodular hyperplasia,[7,8] hepatocellular carcinoma,[9] and peliosis hepatis.[10]

A case of acute hepatic failure has been attributed to danazol in a patient already taking ciclosporin (see below).


1. Ohsawa T, Iwashita S. Hepatitis associated with danazol. *Drug Intell Clin Pharm* 1986; **20:** 889.
2. Boue F, *et al.* Danazol and cholestatic hepatitis. *Ann Intern Med* 1986; **105:** 139–40.
3. Bray GP. *et al.* Resolution of danazol-induced cholestasis with S-adenosylmethionine. *Postgrad Med J* 1993; **69:** 237–9.
4. Fermand JP, *et al.* Danazol-induced hepatocellular adenoma. *Am J Med* 1990; **88:** 529–30.
5. Bork K, *et al.* Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. *Lancet* 1999; **353:** 1066–7.
6. Bork K, Schneiders V. Danazol-induced hepatocellular adenoma in patients with hereditary angio-oedema. *J Hepatol* 2002; **36:** 707–9.
7. Bartley J, *et al.* Hepatocellular adenoma and focal nodular hyperplasia after long-term use of danazol for endometriosis: a case report. *Arch Gynecol Obstet* 2004; **269:** 290–3.
8. Helsing P, Nielsen EW. Hepatocellular focal nodular hyperplasia after danazol treatment for hereditary angio-oedema. *Acta Derm Venereol* 2006; **86:** 272–3.
9. Confavreux C, *et al.* Danazol-induced hepatocellular carcinoma. *QJM* 2003; **96:** 317–18.
10. Makdisi WJ, *et al.* Fatal peliosis of the liver and spleen in a patient with agnogenic myeloid metaplasia treated with danazol. *Am J Gastroenterol* 1995; **90:** 317–8.


**Effects on the pancreas.** There have been reports of pancreatitis in patients receiving danazol.[1,2]


1. Chevalier X, *et al.* Danazol induced pancreatitis and hepatitis. *Clin Rheumatol* 1990; **9:** 239–41.
2. Balasch J, *et al.* Acute pancreatitis associated with danazol treatment for endometriosis. *Hum Reprod* 1994; **9:** 1163–5.


**Effects on the skin and hair.** There have been isolated reports of erythema multiforme occurring in patients given danazol. In 3 cases the reaction developed about 2 weeks after starting danazol, and was effectively managed by stopping danazol and treating with corticosteroids.[1,2]

Hirsutism is a recognised adverse effect of danazol, but is usually mild. Excessive facial hair growth of sudden onset, sufficient to cause distress, has been described in a woman given danazol for mastalgia. The hirsutism improved after stopping the danazol.[3]


1. Gately LE, Andes WA. Danazol and erythema multiforme. *Ann Intern Med* 1988; **109:** 85.
2. Reynolds NJ, Sansom JE. Erythema multiforme during danazol therapy. *Clin Exp Dermatol* 1992; **17:** 140.
3. Zawar V, Sankalecha C. Facial hirsutism following danazol therapy. *Cutis* 2004; **74:** 301–3.


## Precautions

Danazol should be used with caution in conditions that may be adversely affected by fluid retention, such as in cardiovascular, hepatic, and renal disorders; it should be avoided in marked dysfunction. It should also be used with care in patients with diabetes mellitus, polycythaemia, abnormal blood lipids, migraine, or epilepsy. Danazol should not be given to patients with undiagnosed genital bleeding or androgen-dependent tumours. As with other 17α-alkylated compounds, there is an increased risk of liver disorders and liver function should be monitored during therapy. It should not be used in patients with a thromboembolic disorder or a history of thrombosis.

Danazol should not be given during pregnancy because of a possible androgenic effect on the female fetus (see below), and non-hormonal contraception is recommended during treatment. Caution is required in children and adolescents since precocious sexual development may occur in boys and virilisation in girls, and premature epiphyseal closure may occur in both sexes.

In the event of androgenic effects, danazol should be withdrawn, as they may prove irreversible on continued use.

**Breast feeding.** Licensed product information warns that danazol should be avoided in breast-feeding women because of the theoretical potential for androgenic effects in the infant.

**Porphyria.** Danazol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

**Pregnancy.** Reports of masculinisation of female infants born to mothers who had received danazol during pregnancy.[1-3]


1. Shaw RW, Farquhar JW. Female pseudohermaphroditism associated with danazol exposure in utero: case report. *Br J Obstet Gynaecol* 1984; **91:** 386–9.
2. Kingsbury AC. Danazol and fetal masculinization: a warning. *Med J Aust* 1985; **143:** 410–11.
3. Brunskill PJ. The effects of fetal exposure to danazol. *Br J Obstet Gynaecol* 1992; **99:** 212–15.


## Interactions

Therapy with danazol may inhibit the hepatic metabolism of a number of drugs including carbamazepine (see p.475), ciclosporin (see below), and possibly tacrolimus (see p.1845). Danazol may also enhance the effects of warfarin (see Sex Hormones under Warfarin, p.1431). Introduction of danazol appeared to reduce the maintenance requirement for alfacalcidol (see p.1988). Rhabdomyolysis has been attributed to use of danazol with statins (see p.1393).

**Ciclosporin.** Danazol may raise ciclosporin concentrations (see p.1828), possibly by inhibiting its metabolism.

A case of fatal acute hepatic failure due to centrilobular massive hepatic necrosis was attributed to danazol in a patient already taking ciclosporin.[1] Danazol may have raised the ciclosporin concentrations in this case, but the authors speculated that an alternative interaction between the two drugs might have played a role in this reaction to danazol.


1. Hayashi T, *et al.* Fatal acute hepatic failure induced by danazol in a patient with endometriosis and aplastic anemia. *J Gastroenterol* 2001; **36:** 783–6.