doses have been 100 to 600 mg daily; 500 mg has also been given by intramuscular injection, initially twice weekly for 3 months then once weekly for maintenance.

Cachexia. Medroxyprogesterone may improve appetite and food intake, and prevent loss of body-weight in cachexia (p.2115) associated with severe chronic disorders,[1,2] although information is limited.

1. Simons JPFHA, *et al.* Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *J Clin Oncol* 1996; **14:** 1077–84.
2. Simons JPFHA, *et al.* Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer: a randomized, placebo-controlled trial. *Cancer* 1998; **82:** 553–60.

Contraception. Medroxyprogesterone acetate has an established use as a parenteral progestogen-only contraceptive (p.2070). It has also been developed as the progestogenic component of a combined injectable contraceptive and has been investigated as a component of hormonal contraceptives for men.

References.

1. Garza-Flores J, *et al.* Introduction of Cyclofem once-a-month injectable contraceptive in Mexico. *Contraception* 1998; **58:** 7–12.
2. Kaunitz AM, *et al.* Comparative safety, efficacy, and cycle control of Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) and Ortho-Novum 7/7/7 oral contraceptive (norethindrone/ethinyl estradiol triphasic). *Contraception* 1999; **60:** 179–87.
3. Kaunitz AM. Current concepts regarding use of DMPA. *J Reprod Med* 2002; **47** (suppl): 785–9.
4. Turner L, *et al.* Contraceptive efficacy of a depot progestin and androgen combination in men. *J Clin Endocrinol Metab* 2003; **88:** 4659–67.
5. Gu YQ, *et al.* Male hormonal contraception: effects of injections of testosterone undecanoate and depot medroxyprogesterone acetate at eight-week intervals in Chinese men. *J Clin Endocrinol Metab* 2004; **89:** 2254–62.
6. Page ST, *et al.* Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a GnRH antagonist. *J Clin Endocrinol Metab* 2006; **91:** 4374–80.

Epilepsy. Early findings[1] suggested that medroxyprogesterone acetate might be of value in the management of catamenial epilepsy (p.465). In a later review[2] it was suggested that hormonal manipulation with drugs such as medroxyprogesterone should be reserved for highly selected groups under close supervision.

1. Mattson RH, *et al.* Treatment of seizures with medroxyprogesterone acetate: preliminary report. *Neurology* 1984; **34:** 1255–8.
2. Herkes GK. Drug treatment of catamenial epilepsy. *CNS Drugs* 1995; **3:** 260–6.

Male hypersexuality. The anti-androgenic action of medroxyprogesterone has been used for suppression of libido in the control of men with deviant or disinhibited sexual behaviour[1-8] (see Disturbed Behaviour, p.954). Most have received intramuscular medroxyprogesterone acetate; doses of about 300 mg weekly have been used,[3] but ranged from 100 mg each month to 500 mg each week in one report of 5 cases,[8] and up to 750 mg each week in another case.[6] Oral treatment with 30 mg daily was also successful in 1 case.[5]

1. Kiersch TA. Treatment of sex offenders with Depo-Provera. *Bull Am Acad Psychiatry Law* 1990; **18:** 179–87.
2. Weiner MF, *et al.* Intramuscular medroxyprogesterone acetate for sexual aggression in elderly men. *Lancet* 1992; **339:** 1121–2.
3. Kravitz HM, *et al.* Medroxyprogesterone treatment for paraphiliacs. *Bull Am Acad Psychiatry Law* 1995; **23:** 19–33.
4. Britton KR. Medroxyprogesterone in the treatment of aggressive hypersexual behaviour in traumatic brain injury. *Brain Inj* 1998; **12:** 703–7.
5. Brooks JO, Waikar MV. Inappropriate masturbation and schizophrenia. *J Clin Psychiatry* 2000; **61:** 451.
6. Stewart JT. Optimizing antilibidinal treatment with medroxyprogesterone acetate. *J Am Geriatr Soc* 2005; **53:** 359–60.
7. Maletzky BM, *et al.* The Oregon depo-Provera program: a five-year follow-up. *Sex Abuse* 2006; **18:** 303–16.
8. Light SA, Holroyd S. The use of medroxyprogesterone acetate for the treatment of sexually inappropriate behaviour in patients with dementia. *J Psychiatry Neurosci* 2006; **31:** 132–4.

Malignant neoplasms. ***BREAST.*** Progestogens are used as second- or third-choice drugs in the hormonal therapy of advanced breast cancer (p.661). Some references to the use of medroxyprogesterone acetate in advanced breast cancer are cited below.[1-8] Comparative studies have shown that patients respond equally well to medroxyprogesterone and either mepitiostane,[1] aminoglutethimide,[2] or oophorectomy.[3]

1. Izuo M, *et al.* A phase III trial of oral high-dose medroxyprogesterone acetate (MPA) versus mepitiostane in advanced postmenopausal breast cancer. *Cancer* 1985; **56:** 2576–9.
2. Canney PA, *et al.* Randomized trial comparing aminoglutethimide with high-dose medroxyprogesterone acetate in therapy for advanced breast carcinoma. *J Natl Cancer Inst* 1988; **80:** 1147–51.
3. Martoni A, *et al.* High-dose medroxyprogesterone acetate versus oophorectomy as first-line therapy of advanced breast cancer in premenopausal patients. *Oncology* 1991; **48:** 1–6.
4. Muss HB, *et al.* Tamoxifen versus high-dose oral medroxyprogesterone acetate as initial endocrine therapy for patients with metastatic breast cancer: a Piedmont Oncology Association study. *J Clin Oncol* 1994; **12:** 1630–8.
5. Clinton OP, *et al.* A prospective randomized trial to evaluate different oral dose regimens of medroxyprogesterone acetate in women with advanced breast cancer. *Clin Oncol* 1995; **7:** 251–6.
6. Byrne MJ, *et al.* Medroxyprogesterone acetate addition or substitution for tamoxifen in advanced tamoxifen-resistant breast cancer: a phase III randomized trial. *J Clin Oncol* 1997; **15:** 3141–8.
7. Koyama H, *et al.* A randomized controlled comparative study of oral medroxyprogesterone acetate 1,200 and 600 mg in patients with advanced or recurrent breast cancer. *Oncology* 1999; **56:** 283–90.
8. Kloke O, *et al.* Maintenance treatment with medroxyprogesterone acetate in patients with advanced breast cancer responding to chemotherapy: results of a randomized trial. *Breast Cancer Res Treat* 1999; **55:** 51–9.

ENDOMETRIUM. Progestogens are used in the treatment of advanced endometrial carcinoma (p.663) but there are doubts about their value in the earlier stages of disease.[1] Medroxyprogesterone acetate was effective in a rare case of low-grade endometrial stromal sarcoma.[2] It has also been used in a few patients as adjuvant therapy after surgery[3] and for the treatment of metastatic disease.[4]

1. Martin-Hirsch PL, *et al.* Progestagens for endometrial cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 27/06/08).
2. Rand RJ, Lowe JW. Low-grade endometrial stromal sarcoma treated with a progestogen. *Br J Hosp Med* 1990; **43:** 154–6.
3. Amant F, *et al.* Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. *Br J Cancer* 2007; **97:** 1194–9.
4. Pink D, *et al.* Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. *Gynecol Oncol* 2006; **101:** 464–9.

Respiratory disorders. Reviews of the use of medroxyprogesterone acetate in obstructive sleep apnoea have concluded that it has a limited role.[1,2]

Progesterone and, more commonly, medroxyprogesterone acetate are used in the treatment of pulmonary lymphangioleiomyomatosis, a rare disease affecting only women.[3-7] Anecdotal evidence suggests some patients improve or stabilise on treatment, possibly those with chylous effusions or chylous ascites.[8] However, a more rapid decline in lung function has also been observed with progestogen therapy in some groups.[5,6]

Medroxyprogesterone acetate was reported to be effective in treating congenital central hypoventilation syndrome in 2 children.[9] It has also been used in adults with central hypoventilation resulting from brainstem stroke[10] and other causes.[11] Medroxyprogesterone has also been investigated for its effects on respiration in chronic obstructive pulmonary disease, sometimes with acetazolamide.[12-14]

1. Millman RP. Medroxyprogesterone and obstructive sleep apnea. *Chest* 1989; **96:** 225–6.
2. Terra SG, Oberg KC. Medroxyprogesterone acetate in the treatment of obstructive sleep apnea. *Ann Pharmacother* 1997; **31:** 776–8.
3. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999; **54:** 254–64.
4. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; **55:** 1052–7.
5. Johnson SR, *et al.* Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 2004; **59:** 800–3.
6. Taveira-DaSilva AM, *et al.* Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 2004; **126:** 1867–74.
7. Schiavina M, *et al.* Efficacy of hormonal manipulation in lymphangioleiomyomatosis: a 20-year-experience in 36 patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2007; **24:** 39–50.
8. Taylor JR, *et al.* Lymphangioleiomyomatosis: clinical course in 32 patients. *N Engl J Med* 1990; **323:** 1254–60.
9. Milerad J, *et al.* Alveolar hypoventilation treated with medroxyprogesterone. *Arch Dis Child* 1985; **60:** 150–5.
10. Smyth A, Riley M. Chronic respiratory failure: an unusual cause and treatment. *Thorax* 2002; **57:** 835–6.
11. Bootsma GP, *et al.* Chronic respiratory failure. *Thorax* 2003; **58:** 281.
12. Wagenaar M, *et al.* Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; **20:** 1130–7.
13. Wagenaar M, *et al.* Comparison of acetazolamide and medroxyprogesterone as respiratory stimulants in hypercapnic patients with COPD. *Chest* 2003; **123:** 1450–9.
14. Saaresranta T, *et al.* Medroxyprogesterone improves nocturnal breathing in postmenopausal women with chronic obstructive pulmonary disease. *Respir Res* 2005; **6:** 28.

Sickle-cell disease. The frequency of painful crises has been reduced in women with homozygous sickle-cell disease (p.1044) given intramuscular depot medroxyprogesterone acetate,[1,2] and it is now considered to be a suitable contraceptive for this group (see also Sickle-cell Disease, under Precautions of Hormonal Contraceptives, p.2067).

1. de Ceulaer K, *et al.* Medroxyprogesterone acetate and homozygous sickle-cell disease. *Lancet* 1982; **ii:** 229–31.
2. de Abood M, *et al.* Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. *Contraception* 1997; **56:** 313–16.

Preparations

BP 2008: Medroxyprogesterone Injection; Medroxyprogesterone Tablets; ***USP 31:*** Medroxyprogesterone Acetate Injectable Suspension; Medroxyprogesterone Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cycrin†; Depo-Provera†; Farlutale; Livomedrox; Map An; Medrosterona; Veraplex; ***Austral.:*** Depo-Provera; Depo-Ralovera; Medroxyhexal; Provera; Ralovera; ***Austria:*** Depocon; Farlutal; Prodafem; Provera†; ***Belg.:*** Depo-Provera; Farlutal; Provera; Veraplex; ***Braz.:*** Acemedrox; Acetoflux; Contracep; Cycrin; Depo-Provera; Farlutal; Medroxitest; Medroxon; Progesan†; Provera; Tricilon†; ***Canad.:*** Alti-MPA†; Apo-Medroxy; Depo-Provera; Gen-Medroxy; Novo-Medrone; Provera; ratio-MPA; ***Chile:*** Depo-Prodasone; Farlutal; Farlutes; Prodasone; Provera; Sicrit†; ***Cz.:*** Depo-Provera; Femihexal; Medroplex; Provera; Sayana; ***Denm.:*** Depo-Provera; Perlutex; Provera; ***Fin.:*** Depo-Provera; Farlutal; Gestapuran; Lutopolar†; Mepastat; Provera; ***Fr.:*** Depo-Prodasone; Depo-Provera; Farlutal; Gestoral†; ***Ger.:*** Clinofem; Clinovir; Depo-Clinovir; Farlutal†; G-Farlutal†; MPA; MPA Gyn; MPA-beta; MPA-Noury†; ***Gr.:*** Depo-Provera; Farlutal; Gestoral†; Progevera; Provera; ***Hong Kong:*** Depo-Provera; Farlutal; Provera; ***Hung.:*** Depo-Provera; Provera; ***India:*** Depo-Provera; Meprate; ***Indon.:*** Planibu; Prothyra; Provera; Triclofem; Veraplex; ***Irl.:*** Depo-Provera; Provera; ***Israel:*** Aragest; Depo-Provera; Provera; ***Ital.:*** Depo-Provera; Farlutal; Provera; ***Jpn:*** Hysron; ***Malaysia:*** Condep; Depo-Provera; Farlutal†; Non-Preg; Petogen†; Provera; Veraplex; ***Mex.:*** Ciclotal; Cycrin†; Depo-Provera†; Farlutal†; Megestrin†; Megestron; Provera; ***Neth.:*** Depo-Provera; Farlutal†; Megestron; Provera; ***Norw.:*** Depo-Provera; Farlutal; Perlutex; Provera; ***NZ:*** Depo-Provera; Farlutal†; Provera; ***Philipp.:*** Depo-Provera; Depotrust; Lyndavel; Provera; ***Pol.:*** Depo-Provera; Gestomikron; Provera; ***Port.:*** Depo-Provera; Provera; ***Rus.:*** Ciclotal (Циклотал); Depo-Provera (Депопровера); Veraplex (Вераплекс); ***S.Afr.:*** Depo-Provera; Petogen; Provera; ***Singapore:*** Depo-Provera; Farlutal†; Provera; ***Spain:*** Depo-Progevera; Farlutal; Progevera; Progevera 250; ***Swed.:*** Depo-Provera; Farlutal†; Gestapuran; Provera; ***Switz.:*** Depo-Provera; Farlutal; Prodafem; ***Thai.:*** Contracep†; Depo-Gestin; Depo-M; Depo-Progesno; Depo-Progesta; Depo-Provera†; Enaf; Farlutal; Manodepo; Medeton; Pheno-M; Provera; ***Turk.:*** Depo-Provera; Farlutal; ***UK:*** Climanor; Depo-Provera; Farlutal†; Provera; ***USA:*** Amen†; Cycrin†; Depo-Provera; Depo-subQ Provera; Provera; ***Venez.:*** Depo-Provera; Farlutal†; Provera.

Multi-ingredient: ***Arg.:*** Dilena†; Farludiol; Farludiol Ciclo; Periofem Ciclico†; Periofem Continuo†; Premelle Ciclico†; Premelle Continuo†; ***Austral.:*** Menoprem†; Premia; Premia Continuous; Premia Low†; Provelle†; ***Austria:*** Femipak; Filena†; Perennia; Sequennia; ***Belg.:*** Diviplus; Diviva; Premelle Cycle†; Premelle†; Trivina†; ***Braz.:*** Cyclofemina; Dilena; Menosedan Ciclo†; Menosedan Fase†; Menosedan MPA†; 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; Cyclofem†; Enadiol CC; Enadiol MP; Estranova 30 Simple; Estranova CC; Farlupost; Farlutal Estrogeno†; Kilios; Novafac; Novafac 30; Novafac CC; Novafem; Prempak†; Primaquin MP; Primaquin MP Continuo; Profemina CC†; Profemina MP; ***Cz.:*** Cyclo-Premella†; Divina; Diviseq; Indivina; Premella†; ***Denm.:*** Divina; Divina Plus; Indivina; Klimalet; Klimaxil†; Trevina; ***Fin.:*** Divina; Divitren; Indivina; ***Fr.:*** Divina; Diviseq; Duova; Precyclan; ***Ger.:*** Climopax; Climopax Cyclo; Estrafemol; Gianda; Indivina; Osmil; Procyclo; Sisare; Sisare 28; Vitrena†; ***Gr.:*** Divina; Estopause; Premelle; Premelle Cycle; ***Hong Kong:*** Dilena; Premelle; Premelle Cycle; ***Hung.:*** Cyclo-Premella†; Divina; Divitren†; Indivina; Premella†; ***Indon.:*** Cyclofem; ***Irl.:*** Diviseq†; Indivina; Premique; Premique Cycle; ***Israel:*** Meno-MPA†; Premaril MP†; Premaril Plus MP†; ***Ital.:*** Filena; Premelle Combinato; Premelle S†; Premelle Sequenziale†; ***Malaysia:*** Plentiva Cycle 5†; Plentiva†; Premelle; ***Mex.:*** Cyclofemina; Dilena; Premelle; Xofemina; ***Neth.:*** Divina†; Premelle Cycle†; Premelle†; PremelleLite†; ***Norw.:*** Diviseq†; Indivina; ***NZ:*** Menoprem†; Premia Continuous; Premia†; ***Philipp.:*** Premelle; Premelle Cycle; ***Pol.:*** Divina; Diviseq; Indivina; ***Port.:*** Dilena; Medrivas Antibiotico; Premelle Cycle†; Premelle†; ***Rus.:*** Divina (Дивина); Diviseq (Дивисек); Divitren (Дивитрен); Indivina (Индивина); ***S.Afr.:*** Divina; Premelle; Premelle Cycle; Trivina; ***Singapore:*** Premelle Cycle†; Premelle†; ***Spain:*** Medrivas; Medrivas Antib; Perifem; Premelle; Premelle Ciclico; ***Swed.:*** Divina Plus; Divina†; Indivina; Premelle Sekvens†; Premelle†; Trivina; ***Switz.:*** Cyclo-Premella ST; Diviseq; Indivina; OestroTabs Plus Cyclic†; Premella; Premia†; Triaval; ***Thai.:*** Diviseq; Indivina; Premelle Cycle†; Premelle†; ***Turk.:*** Divina; Premelle; Premelle Cycle; ***UK:*** Indivina; Premique; Premique Cycle; Tridestra; ***USA:*** Lunelle†; Premphase; Prempro; ***Venez.:*** Climatrol HT Ciclico; Climatrol HT Continuo; Premelle Ciclico†; Premelle Continuo; Premelle Plus Continuo†.

Megestrol Acetate *(BANM, USAN, rINNM)*

Acetato de megestrol; BDH-1298; Compound 5071; Megestol Asetat; Mégestrol, acétate de; Megestrolacetat; Megestrol-acetát; Megestroli acetas; Megestroliasetaatti; Megestrolio acetatas; Megesztrol-acetát; NSC-71423; SC-10363. 6-Methyl-3,20-dioxopregna-4,6-dien-17α-yl acetate; 17α-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate.

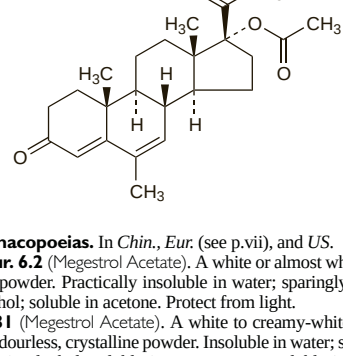
Мегестрола Ацетат

$C_{24}H_{32}O_4$ = 384.5.

CAS — 3562-63-8 (megestrol); 595-33-5 (megestrol acetate).

ATC — G03AC05; G03DB02; L02AB01.

ATC Vet — QG03AC05; QG03DB02; QL02AB01.



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

Ph. Eur. 6.2 (Megestrol Acetate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone. Protect from light.

USP 31 (Megestrol Acetate). A white to creamy-white, essentially odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol; soluble in acetone; very soluble in chloroform; slightly soluble in ether and in fixed oils. Protect from light.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). The weight gain that may occur with megestrol acetate appears to be associated with an increased appetite and food intake rather than with fluid retention. Megestrol acetate may have glucocorticoid effects when given long term.

Effects on carbohydrate metabolism. Megestrol therapy has been associated with hyperglycaemia[1-3] or diabetes mellitus[4] in AIDS patients being treated for cachexia. It has been suggested that megestrol produces peripheral insulin resistance due to a glucocorticoid action.[5]

1. Panwalker AP. Hyperglycemia induced by megestrol acetate. *Ann Intern Med* 1992; **116:** 878.
2. Bornemann M, Johnson AC. Endocrine effects of HIV infection. *N Engl J Med* 1993; **328:** 890.
3. Kilby JM, Tabereaux PB. Severe hyperglycemia in an HIV clinic: preexisting versus drug-associated diabetes mellitus. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 46–50.
4. Henry K, *et al.* Diabetes mellitus induced by megestrol acetate in a patient with AIDS and cachexia. *Ann Intern Med* 1992; **116:** 53–4.
5. Leinung MC, *et al.* Induction of adrenal suppression by megestrol acetate in patients with AIDS. *Ann Intern Med* 1995; **122:** 843–5.

Effects on the musculoskeletal system. Severe pain of the hands similar to carpal tunnel syndrome occurred in 4 women while taking megestrol acetate and melphalan;[1] megestrol appeared to be responsible.

Osteoporosis and vertebral compression fractures occurred in 2 postmenopausal women taking megestrol for anorexia.[2] In both cases there was evidence of adrenocortical insufficiency that recovered after megestrol therapy was stopped, suggesting that the glucocorticoid effect of megestrol may have contributed to the development of osteoporosis.

1. DiSaia PJ, Morrow CP. Unusual side effect of megestrol acetate. *Am J Obstet Gynecol* 1977; **129:** 460–1.
2. Wermers RA, *et al.* Osteoporosis associated with megestrol acetate. *Mayo Clin Proc* 2004; **79:** 1557–61.

Effects on the respiratory system. Hyperpnoea occurred in 2 patients given megestrol acetate 80 mg three times daily.[1]

1. Fessel WJ. Megestrol acetate and hyperpnea. *Ann Intern Med* 1989; **110:** 1034–5.

Glucocorticoid effects. Megestrol has glucocorticoid-like properties that can cause adrenocortical suppression in a significant number of patients.[1-4] There are also reports of adrenal insufficiency severe enough to require replacement therapy with hydrocortisone.[3,5,6]

1. Naing KK, *et al.* Megestrol acetate therapy and secondary adrenal suppression. *Cancer* 1999; **86:** 1044–9.
2. Ron IG, *et al.* A low-dose adrenocorticotropin test reveals impaired adrenal function in cancer patients receiving megestrol acetate therapy. *Eur J Cancer* 2002; **38:** 1490–4.
3. Orme LM, *et al.* Megestrol acetate in pediatric oncology patients may lead to severe, symptomatic adrenal suppression. *Cancer* 2003; **98:** 397–405.
4. Chidakel AR, *et al.* High prevalence of adrenal suppression during acute illness in hospitalized patients receiving megestrol acetate. *J Endocrinol Invest* 2006; **29:** 136–40.
5. Mann M, *et al.* Glucocorticoidlike activity of megestrol: a summary of Food and Drug Administration experience and a review of the literature. *Arch Intern Med* 1997; **157:** 1651–6.
6. Stockheim JA, *et al.* Adrenal suppression in children with the human immunodeficiency virus treated with megestrol acetate. *J Pediatr* 1999; **134:** 368–70.

Porphyria. Megestrol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

As for progestogens in general (see Progesterone, p.2126).

Pharmacokinetics

Megestrol acetate is absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after an oral dose. Megestrol acetate is highly protein bound in plasma. It undergoes hepatic metabolism, with 57 to 78% of a dose being excreted in the urine and 8 to 30% in the faeces.

Uses and Administration

Megestrol acetate is a progestogen structurally related to progesterone (p.2125).

It is used for the palliative treatment of some hormone-dependent malignant neoplasms (see below). Oral doses of 40 to 320 mg daily in divided doses may be given in **endometrial carcinoma**, and doses of 40 mg four times daily or 160 mg once daily may be used in **breast cancer**.

Megestrol acetate is also used in the treatment of **anorexia** and **cachexia** (see below) in patients with cancer or AIDS. The usual dose is 400 to 800 mg daily, as tablets or oral suspension. A suspension of megestrol acetate that has an increased bioavailability is also available (*Megace ES; Par Pharmaceutical, USA*) and is given in a dose of 625 mg in 5 mL daily for anorexia, cachexia, or unexplained significant weight loss in patients with AIDS.

Cachexia. In some patients with severe chronic disorders or malignant neoplasms, anorexia (loss of appetite) forms part of a syndrome of metabolic abnormalities and progressive physical wasting known as cachexia. Improved nutrition and dietary counselling are usually insufficient to reverse cachexia, and drug therapy has been tried to stimulate appetite and promote weight gain.

In **cancer-related cachexia**, corticosteroids are frequently used for appetite stimulation in patients with advanced malignancies, although they do not appear to promote weight gain. However, because their effect is usually temporary, and adverse effects occur with prolonged use,[1-3] they tend to be reserved for short-term treatment in patients with a limited life expectancy of weeks.[4] Megestrol has produced weight gain in some randomised controlled studies,[5] although some of this may result from increase in fat mass rather than increase in lean body-mass.[2,3] It is generally used in patients with a longer life expectancy of months.[4] Similar properties have been reported with medroxyprogesterone.[1] A systematic review[6] concluded that only corticosteroids and the progestogens megestrol and medroxyprogesterone had sufficient evidence to support their use in cancer-related anorexia. Anabolic steroids have also been tried, but further evaluation is necessary:[1,7] a comparison of megestrol or dexamethasone with fluoxymesterone found the latter to be less effective than the progestogen or the corticosteroid.[8] Prokinetic drugs such as metoclopramide may be useful in patients whose symptoms are secondary to decreased gastrointestinal motility,[1,2] although relief of nausea may not necessarily lead to improved caloric intake or appetite.[6] It has been suggested that NSAIDs might inhibit the effects of pro-inflammatory cytokines associated with weight loss in cancer patients. The addition of ibuprofen improved the response to megestrol in one small study,[9] but more work is needed. There has also been interest in the effects of eicosapentaenoic acid, which may inhibit muscle protein degradation, but study results have been mixed[3] and a systematic review[10] concluded that there was insufficient evidence to recommend the use of eicosapentaenoic acid. Further investigation is needed to confirm its clinical effects, possibly using higher doses or treating for longer periods than have been so far reported.[6] Thalidomide was found to attenuate weight loss in a study[11] of patients with advanced pancreatic cancer, but quality of life and duration of survival were not significantly improved. Other drugs studied but with little, if any, benefit include cannabinoids, cyproheptadine and hydrazine.[1,2,6] Other compounds under investigation include the endogenous hormones ghrelin and melatonin.[7]

High-dose megestrol[12-14] or oxandrolone[15-17] are effective in **HIV-related cachexia**, a topic discussed under HIV-associated Wasting, p.858.

1. Mantovani G, *et al.* Managing cancer-related anorexia/cachexia. *Drugs* 2001; **61:** 499–514.
2. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. *CA Cancer J Clin* 2002; **52:** 72–91.
3. Tisdale MJ. Clinical anticachexia treatments. *Nutr Clin Pract* 2006; **21:** 168–74.
4. Jatoi A. Pharmacologic therapy for the cancer anorexia/weight loss syndrome: a data-driven, practical approach. *J Support Oncol* 2006; **4:** 499–502.
5. Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 27/06/08).
6. Yavuzsen T, *et al.* Systematic review of the treatment of cancer-associated anorexia and weight loss. *J Clin Oncol* 2005; **23:** 8500–11.
7. Bossola M, *et al.* Cancer cachexia: it's time for more clinical trials. *Ann Surg Oncol* 2007; **14:** 276–85.
8. Loprinzi CL, *et al.* Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol* 1999; **17:** 3299–3306.
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Hot flushes. Megestrol has been used to treat hot flushes in women with breast cancer (to avoid the potentially tumour-stimulating effects of an oestrogen—see Malignant Neoplasms, under Precautions of HRT, p.2075), as well as in men with hot flushes after orchidectomy or anti-androgen therapy for prostate cancer.[1] Therapy, which involved low oral doses of 20 mg twice daily, was associated with a decrease in frequency of flushes of 50% or more in about three-quarters of all patients. About 3 years after the study had finished, these patients were asked about any ongoing use of megestrol and the occurrence of hot flushes.[2] Although symptoms still occurred in many of the patients taking megestrol, they were less common and less severe than in those who had stopped therapy, which included some who had stopped because of no perceived benefit. In patients taking megestrol, most were on doses of 20 mg or less daily. Information collected about adverse effects of megestrol revealed unexpected reports of chills, but these were described as being not as disabling as the hot flushes had been.

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Malignant neoplasms. Like some other progestogens megestrol acetate is used in endometrial cancer (p.663), and it has been reported to have similar efficacy to anastrozole[1] and tamoxifen[2] in postmenopausal women with advanced breast cancer (p.661). There was no advantage in terms of response or survival in escalating the standard dose of megestrol (160 mg daily) to 800 or 1600 mg daily in a randomised study in women with breast cancer.[3]

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Preparations

BP 2008: Megestrol Tablets;
USP 31: Megestrol Acetate Oral Suspension; Megestrol Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Megace†; Megacorp; Meltonar; Varigestrol; ***Austral.:*** Megace; ***Austria:*** Megace; ***Belg.:*** Megace; ***Braz.:*** Femigestrol; Gynodal; Megestat; ***Canad.:*** Megace; ***Chile:*** Megace; Mestrel†; ***Cz.:*** Megace; Megaplex; ***Denm.:*** Megace; ***Fin.:*** Megace; Megestin†; ***Fr.:*** Megace; ***Ger.:*** Megestat; ***Gr.:*** Megace; ***Hong Kong:*** Megace; ***Hung.:*** Megace; Megesin; ***India:*** Endace; ***Indon.:*** Megace; Megaplex; ***Irl.:*** Megace; ***Israel:*** Megace†; ***Ital.:*** Megace; Megestil; Meprogest†; ***Malaysia:*** Megace; ***Mex.:*** Megace; Mestrel; ***Neth.:*** Megace; ***Norw.:*** Megace; ***NZ:*** Megace; ***Philipp.:*** Megace; ***Pol.:*** Cachexan; Gestar; Megace; Megalia; Megesin; ***Port.:*** Acestrol; Megace; ***Rus.:*** Megaplex (Мегаплекс); ***Singapore:*** Megace; ***Spain:*** Borea; Maygace; Megefren; Megostat†; ***Swed.:*** Megace; ***Switz.:*** Megestat; ***Thai.:*** Megace; Megaplex; Mestrel; ***Turk.:*** Megace; ***UK:*** Megace; ***USA:*** Megace; ***Venez.:*** Megase.

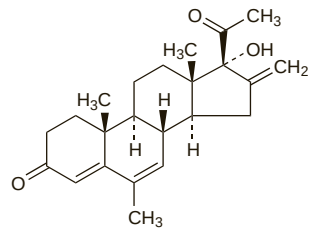
Melengestrol Acetate *(BANM, USAN, rINNM)*

5373; Acetato de melengestrol; BDH-1921; Mélengestrol, Acétate de; Melengestroli Acetas; NSC-70968. 17-Hydroxy-6-methyl-16-methylenepregna-4,6-diene-3,20-dione acetate.

Меленгестрола Ацетат

$C_{25}H_{32}O_4$ = 396.5.

CAS — 5633-18-1 (melengestrol); 2919-66-6 (melengestrol acetate).



(melengestrol)

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Melengestrol Acetate). A white to light yellow, crystalline powder. Insoluble in water; slightly soluble in alcohol; freely soluble in chloroform and in ethyl acetate. Store in airtight containers. Protect from light.