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 in AIDS patients being treated for cachexia. It has been suggested that megestrol produces peripheral insulin resistance due to a glucocorticoid action.5

- 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.
- Kilby JM, Tabereaux PB. Severe hyperglycemia in an HIV clin-ic: 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.
- Leinung MC, et al. Induction of adrenal suppression by megestrol acetate in patients with AIDS. Ann Intern Med 1995; 122:

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. 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 signifi-cant number of patients. ¹⁻⁴ There are also reports of adrenal insufficiency severe enough to require replacement therapy with hydrocortisone. 3,5,6

- Naing KK, et al. Megestrol acetate therapy and secondary adre-nal 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 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.
- 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 hormonedependent 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

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 oc-cur with prolonged use, ¹⁻³ they tend to be reserved for short-term treatment in patients with a limited life expectancy of weeks. 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. Similar properties have been reported with medroxyprogesterone.1 A systematic review6 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 mixed³ and a systematic review¹⁰ 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. Thalidomide was found to attenuate weight loss in a study11 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.

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 On-col 2006; **4:** 499–502.
- 5. Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome. Available in The Cochrane Data-base of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 27/06/08).
- 6. Yavuzsen T, et al. Systematic review of the treatment of cane associated anorexia and weight loss. J Clin Oncol 2005; 23: 8500-11
- 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.
- McMillan DC, et al. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. Br J Cancer 1999; 79: 495–500.
- Dewey A, et al. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Avail able in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 27/06/08).

 11. Gordon JN, et al. Thalidomide in the treatment of cancer
- cachexia: a randomised placebo controlled trial. Gut 2005; 54:
- Von Roenn JH, et al. Megestrol acetate in patients with AIDS-related cachexia. Ann Intern Med 1994; 121: 393–9.
- 13. Oster MH, et al. Megestrol acetate in patients with AIDS and cachexia. Ann Intern Med 1994; 121: 400–408.
- Clarick RH, et al. Megestrol acetate treatment of growth failure in children infected with human immunodeficiency virus. Pedi-
- Strawford A, et al. Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial. JAMA 1999; 281: 1282–90.

- Mwamburi DM, et al. Comparing megestrol acetate therapy with oxandrolone therapy for HIV-related weight loss: similar results in 2 months. Clin Infect Dis 2004; 38: 895–902.
- 17. Grunfeld C, et al. Oxandrolone in the treatment of HIV-associated weight loss in men: a randomized, double-blind, placebo controlled study. J Acquir Immune Defic Syndr 2006; 41:

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.

- Loprinzi CL, et al. Megestrol acetate for the prevention of hot flashes. N Engl J Med 1994; 331: 347–52.
- 2. Quella SK, et al. Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. Cancer 1998; 82:

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 anastrozole1 and tamoxifen2 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

- Buzdar A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer; results of overview analysis of two phase III trials. J Clin Oncol 1996; 14: 2000-11.
- 2. Stuart NSA, et al. A randomised phase III cross-over study of tamoxifen versus megestrol acetate in advanced and recurrent breast cancer. Eur J Cancer 1996; 32A: 1888–92.
- 3. Abrams J, et al. Dose-response trial of megestrol acetate in advanced breast cancer: cancer and Leukemia Group B phase III study 8741. *J Clin Oncol* 1999; **17:** 64–73.

Preparations

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

Proprietary Preparations (details are given in Part 3)

Proprietary Preparations (details are given in Part 3)

Arg.: Megacet, Megacory, Meltonar; Varigestrol; Austral.: Megace; Austria: Megace; Belg.: Megace; Braz.: Fernigestrol; Cyrnodal; Megestat; Canad.: Megace; Chile: Megace; Mestrel†; Cz.: Megace; Megalex; Denm.: Megace; Fin.: Megace; Megace; Mestrel†; Cz.: Megace; Megalex; Gr.: Megace; Fin.: Megace; India: Endace; Indon.: Megace; Megaplex; Irl.: Megace; Israel: Megace; Mestrel; Neth.: Megace; Norw.: Megace; NZ: Megace; Mestrel; Megace; Rus.: Megace; Mestrel; Megace; Mesace; Mesace

Melengestrol Acetate (BANM, USAN, rINNM)

5373; Acetato de melengestrol; BDH-1921; Mélengestrol, Acétate de; Melengestroli Acetas; NSC-70968. 17-Hydroxy-6methyl-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.

Melengestrol acetate is a progestogen that is used as an animal feed in beef heifers to improve feed efficiency, increase the rate of body-weight gain, and suppress oestrus.

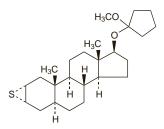
◊ WHO specifies an acceptable daily intake of melengestrol acetate as a residue in foods, and recommends maximum residue limits in various animal tissues. However, it should be noted that, in the EU the use of melengestrol acetate and other steroidal hormones as growth promotors is banned.

FAO/WHO. Evaluation of certain veterinary drug residues in food: sixty-sixth report of the joint FAO/WHO expert committee on food additives. WHO Tech Rep Ser 939 2006. Also available at: http://libdoc.who.int/publications/2006/9241209399_eng.pdf (accessed 24/06/08)

Mepitiostane (rINN) ⊗

Mépitiostane; Mepitiostano; Mepitiostanum; S-10364. 17β-(1-Methoxycyclopentyloxy)- 2α , 3α -epithio- 5α -androstane; Cyclopentanone $2\alpha,3\alpha$ -epithio- 5α -androstan- 17β -yl methyl acetal.

 $C_{25}H_{40}O_2S = 404.6$ CAS - 21362-69-6



Pharmacopoeias. In Jpn.

Mepitiostane has androgenic and anabolic properties (see Testosterone, p.2129) and is given in usual oral doses of 10 mg twice daily for the management of neoplasms of the breast and anaemia associated with renal failure

Preparations

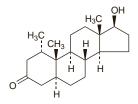
Proprietary Preparations (details are given in Part 3) Jpn: Thioderon.

Mesterolone (BAN, USAN, rINN) \otimes

Mesterolon; Mesterolona; Mesterolonas; Mestérolone; Mesteroloni; Mesterolonum; Meszterolon; NSC-75054; SH-723. 17β-Hydroxy- $I\alpha$ -methyl- 5α -androstan-3-one.

Местеролон

 $C_{20}H_{32}O_2 = 304.5.$ CAS — 1424-00-6. ATC — G03BB01. ATC Vet — QG03BB01.



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

Ph. Eur. 6.2 (Mesterolone). A white or yellowish crystalline powder. Practically insoluble in water; sparingly soluble in acetone, in ethyl acetate, and in methyl alcohol,

Adverse Effects and Precautions

As for androgens in general (see Testosterone, p.2130). Mesterolone is reported not to inhibit gonadotrophin secretion or spermatogenesis.

Pharmacokinetics

Mesterolone is rapidly and almost completely absorbed after an oral dose, producing maximum serum concentrations after about 1.6 hours. It is rapidly metabolised, with an absolute bioavailability of about 3% of the oral dose, and a terminal half-life of 12 to 13 hours. Unlike other androgens (see Testosterone, p.2131), mesterolone is not metabolised to oestrogenic compounds. Mesterolone is bound to serum proteins; about 40% to albumin and 58% to sex-hormone binding globulin. About 77% of the metabolites are excreted in the urine, and about 13% in the faeces.

Uses and Administration

Mesterolone has androgenic properties (see Testosterone, p.2131) but is reported to have less inhibitory effect on intrinsic testicular function than testosterone.

Mesterolone is given orally in the treatment of androgen deficiency or male infertility associated with hypogonadism (p.2079) in initial doses of 75 to 100 mg daily followed by doses of 50 to 75 mg daily for maintenance, in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3) Proprietary Preparations (details are given in Part 3)
Austral: Proviron; Austria: Proviron; Belg.: Proviron; Braz.: Proviron;
Chile: Proviron; Cz.: Proviron; Denm.: Mestoranum†; Fin.: Proviron†;
Ger.: Proviron†; Vistimon†; Gr.: Proviron; Hong Kong: Proviron†; Hung.:
Proviron; India: Proviron; Malaysia: Proviron; Infelon; Proviron; Israel:
Proviron; Ital.: Proviron; Malaysia: Proviron; Pol.: Proviron; Meth.: Proviron; Poli: Proviron; Port.: Proviron;
SAfr:: Proviron; Singapore: Provironum; Spain: Proviron; Thai:: Provironum; Turk.: Proviron; UK: Proviron; Yenez.: Proviron.

Mestranol (BAN, USAN, HNN)

Compound 33355; EE₃ME; Ethinyloestradiol-3-methyl Ether; Mestranoli; Mestranolis; Mestranolum; Mesztranol. 3-Methoxy-19-nor-17 α -pregna-1,3,5(10)-trien-20-yn-17 β -ol.

 $C_{21}H_{26}O_2 = 310.4.$ CAS — 72-33-3.

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

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

USP 31 (Mestranol). A white to creamy-white, odourless, crystalline powder. Insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in chloroform; soluble in dioxan; slightly soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). See also under Hormonal Contraceptives, p.2059.

Porphyria. Mestranol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals or in-vitro systems.

Interactions

See under Hormonal Contraceptives, p.2067.

Pharmacokinetics

Mestranol is readily absorbed from the gastrointestinal tract, and about 70% is rapidly metabolised in the liver to ethinylestradiol (p.2102).

Uses and Administration

Mestranol is a synthetic oestrogen prodrug that is rapidly metabolised to ethinylestradiol; it therefore has actions similar to those of estradiol (see p.2098). It is used as the oestrogen component of combined oral contraceptive preparations (see p.2069) in a usual dose of 50 micrograms daily. The progestogen component is often norethisterone. Mestranol has also been used as the oestrogen component of some preparations for menopausal HRT (see p.2076), although natural oestrogens are often preferred. It has been given in a sequential regimen in a dose of 50 micrograms daily, with a cyclical progestogen.

Preparations

USP 31: Ethynodiol Diacetate and Mestranol Tablets; Norethindrone and

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Austral.: Norinyl-I; Braz.: Biofim†; Megestran†; Canad.: Ortho-Novum 1/50†; Chile: Anovulatorios; Cz.: Menophase†; Ger.: Esticia; Gestamestrol N†; Ovosiston†; Hong Kong: Norinyl-I; Mex.: Lutoral-E; Norace; Norinyl-I); Ortho-Novum†; Secuentex-2 I; NZ: Norinyl-I; S.Afr.: Norinyl-I/28; Thai: Anamai†; UK: Norinyl-I; USA: Necon 1/50; Norinyl I + 50; Ortho-Novum 1/50.

Metenolone (BAN, rINN) ⊗

Metenolon; Metenolona; Méténolone; Metenoloni; Metenolonum; Methenolone. 17β-Hydroxy-1-methyl-5α-androst-1-en-3-

Метенолон $C_{20}H_{30}O_2 = 302.5.$ CAS — 153-00-4. ATC — A14AA04. ATC Vet — QA14AA04.

Metenolone Acetate (BANM, rINNM) ⊗

Acetato de metenolona: Acetato de metilandrostenolona: Méténolone Acétate de Metenoloni Acetas Methenolone Acetate (USAN); NSC-74226; SH-567; SQ-16496. 17β-Hydroxy-1methyl- 5α -androst-I-en-3-one acetate.

Метенолона Ацетат $C_{22}H_{32}O_3 = 344.5.$ CAS — 434-05-9. ATC — A I 4AA04. ATC Vet - QA I 4AA04.

Pharmacopoeias. In Jpn.

Metenolone Enantate (BANM, rINNM) ⊗

Enantato de metenolona; Enantato de metilandrostenolona; Méténolone, Enantate de; Metenoloni Enantas; Methenolone Enanthate (USAN); Methenolone Oenanthate; NSC-64967; SH-601; SQ-16374. 17 β -Hydroxy-1-methyl-5 α -androst-1-en-3-one heptanoate.

Метенолона Энантат $C_{27}H_{42}O_3 = 414.6.$ CAS - 303-42-4. ATC - A14AA04.ATC Vet - QA I 4AA04.

Pharmacopoeias. In Jpn.

Metenolone is an anabolic steroid (see Testosterone, p.2129) that has been used in treating aplastic anaemia, breast cancer, and postmenopausal osteoporosis. Metenolone acetate has been given in oral doses of 100 to 150 mg daily for aplastic anaemia. Intramuscular depot injections of metenolone enantate have been given for osteoporosis in doses of 100 mg every 2 weeks, reducing to once every 3 to 4 weeks after an initial response. The acetate was also used orally in the past for osteoporosis. Intramuscular injections of 100 mg of the enantate every 1 to 2 weeks, or 200 mg every 2 to 3 weeks, have been used in progressive breast cancer.

Preparations

Proprietary Preparations (details are given in Part 3) Austral.: Primobolan; Ger.: Primobolan†; Gr.: Primobolan Depot†; Mex.: Primobolan; S.Afr.: Primobolan; S.Pain: Primobolan Depot.

Multi-ingredient: Ger.: NeyPulpin N (Revitorgan-Dilutionen N Nr 10)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†.

Methandienone (BAN) ⊗

Metandienone (pINN); Metandienon; Metandienona; Métandiénone; Metandienoni; Metandienonum; Methandrostenolone; NSC-42722. 17β-Hydroxy-17α-methylandrosta-1,4-dien-3-one.

Метандиенон $C_{20}H_{28}O_2 = 300.4$. CAS — 72-63-9. ATC — A14AA03; D11AE01. ATC Vet — QA14AA03; QD11AE01.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methandienone: Iron Brew.

Pharmacopoeias. In Pol.