Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Lynestrenol). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol and in acetone. Protect from light.

Profile
Lynestrenol is a progestogen (see Progesterone, p.2125) structurally related to norethisterone that is used alone or as the progestogenic component of oral contraceptives (see p.2058). Typical oral daily doses for contraception are 500 micrograms when used as a progestogen-only preparation, and 0.75 or 2.5 mg when combined with an oestrogen. When used alone for menstrual disorders, doses of 5 to 10 mg daily are given, often as cyclical regimens.

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

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Exluton; ***Austria:*** Orgametril; ***Belg.:*** Orgametril; ***Braz.:*** Exluton; ***Chile:*** Exluton; Linosun; Normalac; ***Cz.:*** Exluton†; Orgametril; ***Denm.:*** Orgametril; ***Fin.:*** Exluton†; Orgametril; ***Fr.:*** Orgametril; ***Ger.:*** Orgametril; ***Gr.:*** Orgametril†; ***Hung.:*** Orgametril; ***Indon.:*** Endometril; Exluton; ***Mex.:*** Exluton; ***Neth.:*** Exluton; Orgametril; ***Norw.:*** Exlutona†; ***Philipp.:*** Daphne; Exluton; ***Pol.:*** Orgametril; ***Port.:*** Exluton†; Orgametril†; ***Rus.:*** Exluton (Экслютон); ***S.Afr.:*** Exluton†; ***Spain:*** Orgametril; ***Swed.:*** Exlutena; Orgametril; ***Thai.:*** Exluton; ***Turk.:*** Orgametril; ***Venez.:*** Exluton; Normalac.

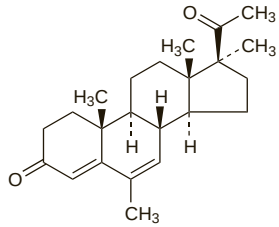
Multi-ingredient: ***Arg.:*** Lindiol†; ***Braz.:*** Anacyclin†; Ovoresta; ***Chile:*** Anovulatorios; ***Cz.:*** Restovar†; ***Ger.:*** Lyn-ratiopharm-Sequenz; Ovoresta M; ***Neth.:*** Lyndiol†; Ministat; Ovostat†; ***Swed.:*** Restovar; ***Thai.:*** Lyndiol†.

Medrogestone *(BAN, USAN, rINN)*

AY-62022; Medrogeston; Medrogestona; Médrogestone; Medrogestoni; Medrogestonum; Metrogestone; NSC-123018; R-13-615. 6,17α-Dimethylpregna-4,6-diene-3,20-dione.

Медрогестон

$C_{23}H_{32}O_2$ = 340.5.
CAS — 977-79-7.
ATC — G03DB03.
ATC Vet — QG03DB03.



Profile
Medrogestone is a progestogen structurally related to progesterone (p.2125) that is used in the treatment of menstrual disorders, and as the progestogen in menopausal HRT (see p.2071). It is usually given orally in daily doses of 5 to 10 mg, generally in a cyclical regimen. Higher doses were used in the treatment of endometrial carcinoma, prostatic hyperplasia, and breast disorders including carcinoma. It has also been used for threatened or recurrent miscarriage, but such use is not recommended unless there is proven progesterone deficiency.

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Colpron; ***Belg.:*** Colpro†; ***Fr.:*** Colprone; ***Ger.:*** Prothil; ***Hong Kong:*** Colprone†; ***Ital.:*** Colprone†; ***S.Afr.:*** Colpro†; ***Spain:*** Colpro†; ***Switz.:*** Colpro†.

Multi-ingredient: ***Austria:*** Premarin compositum†; Premarin Plus; ***Belg.:*** Premplus†; ***Cz.:*** Presomen Compositum†; ***Ger.:*** Presomen Compositum; ***Hong Kong:*** Prempak†; ***Ital.:*** Prempak†; ***Malaysia:*** Prempak†; ***Neth.:*** Premarin Plus†; ***Port.:*** Premarin Plus†; ***S.Afr.:*** Prempak N; ***Switz.:*** Premarin Plus†.

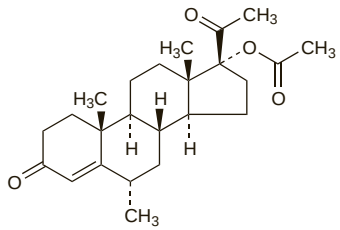
Medroxyprogesterone Acetate

(BANM, rINNM)

Acetato de medroxiprogesterona; Medroksiprogesteron Asetat; Medroksiprogesteroniasetaatti; Medroksiprogesterono acetatas; Medroksyprogesteronu octan; Medroxiprogesteronacetat; Medroxiprogeszteron-acetát; Medroxyprogesteron-acetát; Médroxyprogestérone, acétate de; Medroxyprogesteroni acetas; Methylacetoxyprogesterone; Metipregnone; NSC-26386. 6α-Methyl-3,20-dioxopregn-4-en-17α-yl acetate; 17α-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate.

Медроксипрогестерона Ацетат

$C_{24}H_{34}O_4$ = 386.5.
CAS — 520-85-4 (medroxyprogesterone); 71-58-9 (medroxyprogesterone acetate).
ATC — G03AC06; G03DA02; L02AB02.
ATC Vet — QG03AC06; QG03DA02; QL02AB02.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Medroxyprogesterone Acetate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.
USP 31 (Medroxyprogesterone Acetate). A white to off-white, odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone and in dioxan; freely soluble in chloroform; slightly soluble in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions
As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059. Medroxyprogesterone acetate may have glucocorticoid effects when given long term at high doses.

Breast feeding. Medroxyprogesterone is reported to be distributed into breast milk when given as a depot progestogen-only contraceptive.[1] No adverse effects have been seen in breast-fed infants of mothers given medroxyprogesterone, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding. Progestogen-only parenteral contraceptives should not be used until 6 weeks after birth if the woman is breast feeding (see Breast Feeding under Hormonal Contraceptives, p.2066).

1. Schwallie PC. The effect of depot-medroxyprogesterone acetate on the fetus and nursing infant: a review. *Contraception* 1981; **23:** 375–86.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Carcinogenicity. The risk of various cancers associated with the use of depot medroxyprogesterone acetate as a contraceptive has been evaluated by WHO.[1] Overall, there was no increase in risk of breast cancer, although there is some evidence that current or recent use may be associated with a slight increase in risk (see also p.2059). There was no significant increased risk of cervical cancer (see also p.2060), and a protective effect against endometrial cancer (see p.2060). In contrast to combined oral contraceptives, there was no evidence of a protective effect against ovarian cancer (p.2061).

1. Anonymous. Depot-medroxyprogesterone acetate (DMPA) and cancer: memorandum from a WHO meeting. *Bull WHO* 1993; **71:** 669–76.

Effects on bone density. Use of medroxyprogesterone acetate as a parenteral progestogen-only contraceptive has been associated with reductions in bone density (see under Effects on the Musculoskeletal System, p.2064). This effect has also been reported after oral doses for menstrual disorders,[1] and is thought to be due to medroxyprogesterone-induced oestrogen deficiency.

1. Cundy T, *et al.* Short-term effects of high dose oral medroxyprogesterone acetate on bone density in premenopausal women. *J Clin Endocrinol Metab* 1996; **81:** 1014–17.

Effects on the skin. Acute local skin necrosis has been reported[1] after the intramuscular injection of medroxyprogesterone acetate as a depot contraceptive. A case of pigmented purpura on the lower legs, occurring about 4 months after starting medroxyprogesterone acetate injections, has been described.[2]

1. Clark SM, Lanigan SW. Acute necrotic skin reaction to intramuscular Depo-Provera . *Br J Dermatol* 2000; **143:** 1356–7.
2. Tsao H, Lerner LH. Pigmented purpuric eruption associated with injection medroxyprogesterone acetate. *J Am Acad Dermatol* 2000; **43:** 308–10.

Glucocorticoid effects. There have been reports of Cushing's syndrome induced by medroxyprogesterone acetate in patients receiving long-term therapy with high doses for the treatment of malignant neoplasms[1-5] or paraphilia.[6] Cushingoid symptoms regressed when treatment was stopped. Medroxyprogesterone possesses glucocorticoid activity and there is a risk of adrenal insufficiency during periods of stress or after sudden withdrawal of treatment. Some[4] consider that patients should be monitored for glucose intolerance and adrenal insufficiency during treatment.

1. Siminoski K, *et al.* The Cushing syndrome induced by medroxyprogesterone acetate. *Ann Intern Med* 1989; **111:** 758–60.
2. Donckier JE, *et al.* Cushing syndrome and medroxyprogesterone acetate. *Lancet* 1990; **335:** 1094.
3. Grenfell A, *et al.* Cushing's syndrome and medroxyprogesterone acetate. *Lancet* 1990; **336:** 256.
4. Merrin PK, Alexander WD. Cushing's syndrome induced by medroxyprogesterone. *BMJ* 1990; **301:** 345.
5. Shotliff K, Nussey SS. Medroxyprogesterone acetate induced Cushing's syndrome. *Br J Clin Pharmacol* 1997; **44:** 304.
6. Krueger RB, *et al.* Prescription of medroxyprogesterone acetate to a patient with pedophilia, resulting in Cushing's syndrome and adrenal insufficiency. *Sex Abuse* 2006; **18:** 227–8.

Porphyria. Medroxyprogesterone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients. However, for a reference to the use of medroxyprogesterone acetate with buserelin acetate in the prevention of premenstrual exacerbations of porphyria in 2 women, see p.2084.

Interactions
As for progestogens in general (see Progesterone, p.2126). Aminoglutethimide markedly reduces plasma concentrations of medroxyprogesterone so that an increase in medroxyprogesterone dosage is likely to be required.

Pharmacokinetics
Medroxyprogesterone is absorbed from the gastrointestinal tract. In the blood, it is highly protein bound, principally to albumin. It is metabolised in the liver and excreted mainly as glucuronide conjugates in the urine and faeces. It has a half-life of about 16 to 30 hours after oral doses; the half-life may be as long as 50 days after intramuscular injection. Medroxyprogesterone is reported to be distributed into breast milk.

Uses and Administration
Medroxyprogesterone acetate is a progestogen structurally related to progesterone, with actions and uses similar to those of the progestogens in general (see Progesterone, p.2126). It is given orally or, for prolonged action, as an aqueous suspension by intramuscular or subcutaneous injection, depending on the product.

It is used for the treatment of **menorrhagia** (p.2126) and **secondary amenorrhoea** in oral doses of 2.5 to 10 mg daily for 5 to 10 days starting on the assumed or calculated 16th to 21st day of the menstrual cycle, although treatment may begin on any day in secondary amenorrhoea.

In the treatment of mild to moderate **endometriosis** (p.2091) usual oral doses are 10 mg three times daily for 90 consecutive days, or 50 mg weekly or 100 mg every 2 weeks by intramuscular injection for at least 6 months. An alternative formulation used for the treatment of pain associated with endometriosis is given in a dose of 104 mg in 0.65 mL by subcutaneous injection once every 12 to 14 weeks.

Medroxyprogesterone acetate is also given by injection as a **contraceptive** (see under Hormonal Contraceptives, p.2069). As a progestogen-only contraceptive an intramuscular dose of 150 mg is given every 12 or 13 weeks. A combined contraceptive injection containing medroxyprogesterone acetate 25 mg with estradiol cipionate 5 mg is given monthly as an intramuscular injection. An alternative formulation used as a progestogen-only contraceptive is given as a dose of medroxyprogesterone acetate 104 mg in 0.65 mL by subcutaneous injection once every 12 to 14 weeks.

When used as the progestogen component of **menopausal HRT** (see p.2076), medroxyprogesterone acetate is given orally in a variety of regimens including 1.5, 2.5, or 5 mg daily continuously, 5 or 10 mg daily for 12 to 14 days of a 28-day cycle, and 20 mg daily for 14 days of a 91-day cycle.

Medroxyprogesterone acetate may also be used in the palliative treatment of some hormone-dependent malignant neoplasms. In **breast carcinoma** (see below) oral doses of 0.4 to 1.5 g daily may be given, although doses up to 2 g daily have been used in the past. Intramuscular medroxyprogesterone acetate has been given in initial doses of 500 mg daily for 4 weeks, then in maintenance doses twice weekly. In **endometrial** (below) and **renal carcinoma** (p.667) oral doses have ranged from 200 to 600 mg daily. Initial doses of 0.6 to 1.2 g weekly have been given by intramuscular injection, reducing to a maintenance schedule of as little as 450 mg monthly. In **prostatic carcinoma** (p.671) oral