2. Krueger RB, Kaplan MS. Depot-leuprolide acetate for treatment of paraphilias: a report of twelve cases. *Arch Sex Behav* 2001; **30:** 409–22.
3. Saleh FM, *et al.* Treatment of paraphilia in young adults with leuprolide acetate: a preliminary case report series. *J Forensic Sci* 2004; **49:** 1343–8.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p.2091) but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' hormone replacement therapy can be used to prevent this.

References to the use of leuprorelin.

1. Hornstein MD, *et al.* Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Obstet Gynecol* 1998; **91:** 16–24.
2. Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. *Obstet Gynecol* 1999; **93:** 51–8.
3. Takeuchi H, *et al.* A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis. *J Obstet Gynaecol Res* 2000; **26:** 325–31.
4. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol* 2002; **99:** 709–19.
5. Rotondi M, *et al.* Depot leuprorelin acetate versus danazol in the treatment of infertile women with symptomatic endometriosis. *Eur J Gynaecol Oncol* 2002; **23:** 523–6.

Fibroids. Gonadorelin analogues may be of some benefit as an adjunct or alternative to surgery in women with uterine fibroids (p.2107), although there has been some concern that this might complicate the diagnosis of malignancy.

References to the use of leuprorelin.

1. Friedman AJ, *et al.* Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. *Obstet Gynecol* 1991; **77:** 720–5.
2. Friedman AJ, *et al.* Long-term medical therapy for leiomyomata uteri: a prospective, randomized study of leuprolide acetate depot plus either oestrogen-progestin or progestin 'add-back' for 2 years. *Hum Reprod* 1994; **9:** 1618–25.
3. Zullo F, *et al.* A prospective randomized study to evaluate leuprolide acetate treatment before laparoscopic myomectomy: efficacy and ultrasonographic predictors. *Am J Obstet Gynecol* 1998; **178:** 108–112.
4. Scialli AR, Levi AJ. Intermittent leuprolide acetate for the nonsurgical management of women with leiomyomata uteri. *Fertil Steril* 2000; **74:** 540–6.
5. Jasonni VM, *et al.* Randomized double-blind study evaluating the efficacy on uterine fibroids shrinkage and on intra-operative blood loss of different length of leuprolide acetate depot treatment before myomectomy. *Acta Obstet Gynecol Scand* 2001; **80:** 956–8.

Hirsutism. The mainstay of drug treatment for hirsutism (p.2089) has been an anti-androgen, usually cyproterone acetate or spironolactone. Although gonadorelin analogues have been used, and are effective, they must be given parenterally or nasally and may produce menopausal effects, notably osteoporosis.

References to the use of leuprorelin.

1. Elkind-Hirsch KE, *et al.* Combination gonadotropin-releasing hormone agonist and oral contraceptive therapy improves treatment of hirsute women with ovarian hyperandrogenism. *Fertil Steril* 1995; **63:** 970–8.
2. Azziz R, *et al.* Leuprolide and estrogen versus oral contraceptive pills for the treatment of hirsutism: a prospective randomized study. *J Clin Endocrinol Metab* 1995; **80:** 3406–11.
3. Ciotta L, *et al.* Clinical and hormonal effects of gonadotropin-releasing hormone agonist plus an oral contraceptive in severely hirsute patients with polycystic ovary disease. *Fertil Steril* 1996; **65:** 61–7.
4. Bayhan G, *et al.* A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism. *Clin Exp Obstet Gynecol* 2000; **27:** 203–6.

Infertility. Gonadorelin analogues are used in the treatment of infertility—see p.2080.

References to the use of leuprorelin.

1. Stone BA, *et al.* Gonadotrophin and estradiol levels during ovarian stimulation in women treated with leuprolide acetate. *Obstet Gynecol* 1989; **73:** 990–5.
2. Sathanandan M, *et al.* Adjuvant leuprolide in normal, abnormal, and poor responders to controlled ovarian hyperstimulation for in vitro fertilization/gamete intrafallopian transfer. *Fertil Steril* 1989; **51:** 998–1006.
3. Filicori M, *et al.* Different gonadotropin and leuprorelin ovulation induction regimens markedly affect follicular fluid hormone levels and folliculogenesis. *Fertil Steril* 1996; **65:** 387–93.
4. Surrey ES, *et al.* Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis. *Fertil Steril* 2002; **78:** 699–704.

Malignant neoplasms. Gonadorelin analogues are used as an alternative to orchidectomy in the management of advanced malignant neoplasms of the prostate (p.671). Such therapy is as effective as orchidectomy in prolonging survival;[1] combination of leuprorelin or other gonadorelin analogues with nonsteroidal anti-androgens to produce maximal androgen blockade produces only modest additional benefit.[2] Intermittent maximal androgen blockade is being studied in an attempt to improve results, and leuprorelin is also under investigation as neoadjuvant therapy in localised disease.[3] Leuprorelin is also used for ovarian ablation[4] in premenopausal women with breast cancer (p.661).

There are also isolated reports of endometrial cancer (p.663),[5] and ovarian cancer[6] responding to leuprorelin, but the role of the gonadorelin analogues in these conditions is much less well established.

1. Seidenfeld J, *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; **132:** 566–77.
2. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000; **355:** 1491–8.
3. Persad R. Leuprorelin acetate in prostate cancer: a European update. *Int J Clin Pract* 2002; **56:** 389–96.
4. Schmid P, *et al.* Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprorelin acetate as adjuvant treatment of node-positive, premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuprorelin Acetate). *Anticancer Res* 2002; **22:** 2325–32.
5. Noci I, *et al.* Longstanding survival without cancer progression in a patient affected by endometrial carcinoma treated primarily with leuprolide. *Br J Cancer* 2001; **85:** 333–6.
6. Paskeviciute L, *et al.* No rules without exception: long-term complete remission observed in a study using a LH-RH agonist in platinum-refractory ovarian cancer. *Gynecol Oncol* 2002; **86:** 297–301.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p.2081).

References to the use of leuprorelin.

1. Lee PA, *et al.* Effects of leuprolide in the treatment of central precocious puberty. *J Pediatr* 1989; **114:** 321–4.
2. Clemons RD, *et al.* Long-term effectiveness of depot gonadotropin-releasing hormone analogue in the treatment of children with central precocious puberty. *Am J Dis Child* 1993; **147:** 653–7.
3. Carel JC, *et al.* Treatment of central precocious puberty with depot leuprorelin. *Eur J Endocrinol* 1995; **132:** 699–704.
4. Carel J-C, *et al.* Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). *J Clin Endocrinol Metab* 2002; **87:** 4111–16.
5. Tanaka T, *et al.* Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function: the TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J Clin Endocrinol Metab* 2005; **90:** 1371–6.

Premenstrual syndrome. For reference to the use of leuprorelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug therapy, see under Gonadorelin, p.2108.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Eligard; Lectrum; Lupron; Reliser†; ***Austral.:*** Eligard; Lucrin; ***Austria:*** Enantone; Trenantone; ***Belg.:*** Depo-Eligard; Lucrin; ***Braz.:*** Lectrum; Lorelin; Lupron; Reliser; ***Canad.:*** Eligard; Lupron; ***Chile:*** Lupron; ***Cz.:*** Eligard; Lucrin; ***Denm.:*** Enanton†; Procren; ***Fin.:*** Eligard; Enanton; Procren; ***Fr.:*** Eligard; Enantone; Lucrin†; ***Ger.:*** Eligard; Enantone; Enantone-Gyn; Trenantone; Uno-Enantone†; ***Gr.:*** Daronda; Elityran; Leuprol; ***Hong Kong:*** Enantone; Lorelin; Lucrin†; ***Hung.:*** Eligard; Lucrin; ***India:*** Lupride; ***Indon.:*** Endrolin; Lectrum; Tapros; ***Irl.:*** Prostap; ***Israel:*** Lucrin; ***Ital.:*** Enantone; ***Jpn:*** Leuplin; Lupron; ***Malaysia:*** Lucrin; ***Mex.:*** Lectrum; Lorelin; Lucrin; Reliser†; ***Neth.:*** Daronda; Eligard; Lucrin; ***Norw.:*** Enanton; Procren; ***NZ:*** Eligard; Lucrin; ***Philipp.:*** Luprolex; ***Pol.:*** Eligard; Lucrin Depot; ***Port.:*** Eligard; Lucrin; ***Rus.:*** Lucrin (Люкрин); ***S.Afr.:*** Lucrin; ***Singapore:*** Lucrin; ***Spain:*** Eligard; Ginecrin; Procrin; ***Swed.:*** Eligard; Enanton; Procren; ***Switz.:*** Eligard; Lucrin; ***Thai.:*** Enantone; ***Turk.:*** Lucrin; ***UK:*** Prostap; ***USA:*** Eligard; Lupron; Viadur†; ***Venez.:*** Lupron; Reliser†.

Luteinising Hormone ⊗

Human Interstitial-cell-stimulating Hormone; ICSH; LH; Lutropin; Lutropina.

CAS — 9002-67-9; 39341-83-8 (human).

Lutropin Alfa *(BAN, USAN, rINN)* ⊗

Lutropina alfa; Lutropine Alfa; Lutropinum Alfa.

Лутропин Альфа

CAS — 152923-57-4 (lutropin alfa); 56832-30-5 (α subunit); 53664-53-2 (β subunit).
ATC — G03GA07.
ATC Vet — QG03GA07.

Units

35 units of human pituitary luteinising hormone are contained in about 5.8 micrograms (with 1 mg of human albumin, 5 mg of mannitol, and 1 mg of sodium chloride) in one ampoule of the second International Standard (1988).

10 units of the alpha subunit of human pituitary luteinising hormone are contained in about 10 micrograms (with 0.5 mg of human albumin, 2.5 mg of lactose, and 45 micrograms of sodium chloride) in one ampoule of the first International Standard (1984).

10 units of the beta subunit of human pituitary luteinising hormone are contained in 10 micrograms (with 0.5 mg of human albumin, 2.5 mg of lactose, and 45 micrograms of sodium chloride) in one ampoule of the first International Standard (1984).

189 units of recombinant human luteinising hormone are contained in about 8.8 micrograms (with 2 mg of human albumin, 10 mg of lactose, and 8.9 mg of sodium chloride) in one ampoule of the first International Standard (2003).

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p.2109.

Pharmacokinetics

The absolute bioavailability of lutropin alfa after subcutaneous doses is about 60%, and the terminal half-life is at least 10 to 12 hours.

Uses and Administration

Luteinising hormone (LH) is secreted with follicle-stimulating hormone (FSH) (p.2104), another gonadotrophin, by the anterior pituitary lobe.

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova. As the follicle develops it produces oestrogen in increasing amounts which at mid-cycle stimulates the release of LH. This causes rupture of the follicle with ovulation and converts the follicle into the corpus luteum which secretes progesterone. In men, luteinising hormone stimulates the interstitial cells of the testis to secrete testosterone, which in turn has a direct effect on the seminiferous tubules.

Gonadotrophic substances with luteinising or follicle-stimulating activity or both are used in the treatment of infertility (p.2080), chiefly in females but also in males. Such substances include chorionic gonadotrophin (p.2085) which possesses LH activity and human menopausal gonadotrophins (p.2110) which possess both LH and FSH activity.

Lutropin alfa is a recombinant human luteinising hormone used to induce ovulation in women with severe deficiency of luteinising and follicle-stimulating hormones. It is used at the same time as a preparation with follicle-stimulating activity, usually follitropin alfa. The dosage and schedule of treatment must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. Treatment is usually begun with 75 units of lutropin alfa daily by subcutaneous injection for 7 to 14 days, accompanied by FSH. If there is no response, the FSH dosage may be increased at 7- or 14-day intervals until an adequate but not excessive response is achieved. A treatment cycle of up to 5 weeks may be needed. Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation. These patients are generally amenorrhoeic and treatment may be started at any time.

◊ References.

1. The European Recombinant Human LH Study Group. Recombinant human luteinizing hormone (LH) to support recombinant human follicle-stimulating hormone (FSH)-induced follicular development in LH- and FSH-deficient anovulatory women: a dose-finding study. *J Clin Endocrinol Metab* 1998; **83:** 1507–14.
2. Burgués S, The Spanish Collaborative Group on Female Hypogonadotrophic Hypogonadism. The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group I anovulation: evidence from a multicentre study in Spain. *Hum Reprod* 2001; **16:** 2525–32.
3. The European Recombinant LH Study Group. Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. *J Clin Endocrinol Metab* 2001; **86:** 2607–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Luveris; ***Austral.:*** Luveris; ***Belg.:*** Luveris†; ***Braz.:*** Luveris; ***Chile:*** Luveris†; ***Cz.:*** Luveris; ***Denm.:*** Luveris; ***Fin.:*** Luveris; ***Fr.:*** Luveris; ***Ger.:*** Luveris; ***Gr.:*** Luveris; ***Hong Kong:*** Luveris; ***Hung.:*** Luveris; ***Indon.:*** Luveris; ***Irl.:*** Luveris; ***Israel:*** Luveris; ***Ital.:*** Luveris; ***Malaysia:*** Luveris; ***Mex.:*** Luveris; ***Neth.:*** Luveris; ***Norw.:*** Luveris; ***NZ:*** Luveris; ***Philipp.:*** Luveris; ***Pol.:*** Luveris; ***Port.:*** Luveris; ***Rus.:*** Luveris (Лувэрис); ***Singapore:*** Luveris; ***Spain:*** Luveris; ***Swed.:*** Luveris; ***Switz.:*** Luveris; ***Thai.:*** Luveris; ***Turk.:*** Luveris; ***UK:*** Luveris; ***USA:*** Luveris; ***Venez.:*** Luveris.

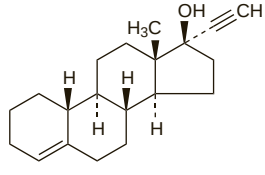
Multi-ingredient: ***Cz.:*** Pergoveris; ***Port.:*** Pergoveris; ***UK:*** Pergoveris.

Lynestrenol *(BAN, USAN, rINN)*

Ethinylestrenol; Etinilestrenol; Linestrenol; Linestrenolis; Linesztrenol; Linoestrenol; Lynenol; Lynestrénol; Lynestrenoli; Lynestrenolum; Lynoestrenol; NSC-37725. 19-Nor-17α-pregn-4-en-20-yn-17β-ol.

Линэстренол

$C_{20}H_{28}O$ = 284.4.
CAS — 52-76-6.
ATC — G03AC02; G03DC03.
ATC Vet — QG03AC02; QG03DC03.



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.

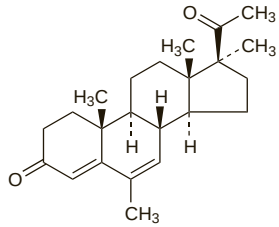
Multi-ingredient: ***Arg.:*** Lindiol†; ***Braz.:*** Anacyclin†; Ovoresta; ***Chile:*** Anovulatorios; ***Cz.:*** Restovar†; ***Ger.:*** Lyn-ratiopharm-Sequenz; Ovoresta M; ***Neth.:*** Lyndiol†; Ministat; Ovostat†; ***Swed.:*** Restovar; ***Thai.:*** Lyndiol†.

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†.

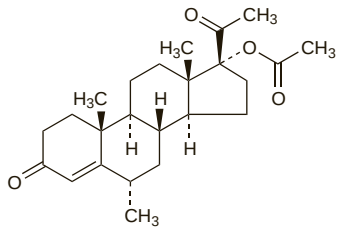
Medroxyprogesterone Acetate

(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