plus chorionic gonadotrophin.[2,3] In another case in which thrombosis followed the use of human menopausal gonadotrophins alone, hereditary activated protein C resistance and smoking may have been contributing factors.[4]

1. Kemmann E, *et al*. Adnexal torsion in menotropin-induced pregnancies. *Obstet Gynecol* 1990; **76:** 403–6.
2. Kaaja R, *et al.* Severe ovarian hyperstimulation syndrome and deep venous thrombosis. *Lancet* 1989; **ii:** 1043.
3. Sobande AA, *et al*. Ovarian hyperstimulation syndrome and deep vein thrombosis. *Saudi Med J* 2000; **21:** 783–4.
4. Ludwig M, *et al*. Deep vein thrombosis during administration of HMG for ovarian stimulation. *Arch Gynecol Obstet* 2000; **263:** 139–41.

Precautions

Human menopausal gonadotrophins should not be given to pregnant patients. Use should be avoided in patients with abnormal genital bleeding, hormone sensitive malignancies such as those of the breast, uterus, prostate, ovaries or testes, or ovarian cysts or enlargement not caused by the polycystic ovary syndrome. Pituitary or hypothalamic lesions, adrenal or thyroid disorders, and hyperprolactinaemia should be treated appropriately to exclude them as causes of infertility before attempting therapy with human menopausal gonadotrophins. Patients who experience ovarian enlargement are at risk of rupture; pelvic examinations should be avoided or carried out with care and the recommendation has been made that sexual intercourse should be avoided while there is such a risk.

There is a risk of multiple births.

Interactions

In women who show evidence of excessive ovarian stimulation while receiving human menopausal gonadotrophins the use of drugs with luteinising-hormone (LH) activity increases the risk of ovarian hyperstimulation syndrome.

Uses and Administration

Human menopausal gonadotrophins possess both follicle-stimulating hormone (FSH) activity (see p.2104) and luteinising hormone (LH) activity (see p.2112).

Human menopausal gonadotrophins are used in the treatment of male and female infertility due to hypogonadism. In anovulatory infertility unresponsive to clomifene, human menopausal gonadotrophins are given to induce follicular maturation and are followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation, a topic discussed further on p.2080.

The dosage and schedule of treatment for **female infertility** 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. Human menopausal gonadotrophins may be given daily by intramuscular or subcutaneous injection to provide a dose of 75 to 150 units of FSH and gradually adjusted if necessary until an adequate response is achieved. Treatment is then stopped and followed after 1 or 2 days by single doses of chorionic gonadotrophin 5000 to 10 000 units (see p.2085). In menstruating patients treatment should be started within the first 7 days of the menstrual cycle. In the UK it has been suggested that the treatment course should be abandoned if no response is seen in 3 weeks although in the US the manufacturers recommend that an individual course should not exceed 12 days. This course may be repeated at least twice more if necessary.

An alternative schedule is to give three equal doses by intramuscular or subcutaneous injection, each providing 225 to 375 units of FSH on alternate days followed by chorionic gonadotrophin one week after the first dose.

In IVF and other assisted conception techniques, human menopausal gonadotrophins are used with chorionic gonadotrophin and sometimes also clomifene citrate or a gonadorelin analogue. Stimulation of follicular growth is produced by human menopausal gonadotrophins given by intramuscular or subcutaneous injection, in a dose providing 75 to 300 units of FSH daily, usually beginning on the 2nd or 3rd day of the menstrual cycle. Treatment is continued until an adequate response is obtained and the final injection of human menopausal gonadotrophins is followed 1 to 2 days later with up to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is carried out about 32 to 36 hours later.

In **men with infertility** due to hypogonadotrophic hypogonadism (see Infertility, p.2080), spermatogenesis is stimulated with chorionic gonadotrophin and then human menopausal gonadotrophins are added in a dose of 75 or 150 units of FSH two or three times weekly by intramuscular or subcutaneous injection. Treatment should be continued for at least 3 or 4 months.

Infertility. Systematic reviews have not found evidence of a significant difference in efficacy for human menopausal gonadotrophins compared with urinary-derived gonadotrophins in women with anovulatory infertility[1] (p.2080), or compared with recombinant follicle-stimulating hormone in assisted reproduction cycles.[2] UK guidelines[3] consider that human menopausal gonadotrophins, urinary follicle-stimulating hormone, and recombinant follicle-stimulating hormone are equally effective in achieving pregnancy for women with ovulatory disorders, such as polycystic ovary syndrome, and for IVF treatment.

1. Nugent D, *et al.* Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 16/09/05).
2. Van Wely M, *et al.* Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
3. National Collaborating Centre for Women's and Children's Health/NICE. Fertility: assessment and treatment for people with fertility problems. February 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 28/07/08)

Preparations

BP 2008: Menotrophin Injection;
USP 31: Menotropins for Injection.

Proprietary Preparations (details are given in Part 3)

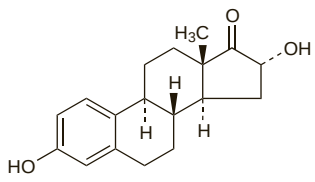
Arg.: HMG Ferring; Lifecell; Menopur; Pergonal†; ***Austral.:*** Humegon; ***Austria:*** Menopur; ***Belg.:*** Menopur; ***Braz.:*** Menogon†; Menopur†; Merional-HMG†; Pergonal; ***Canad.:*** Humegon†; Pergonal†; Repronex; ***Chile:*** Menopur; Pergonal†; ***Cz.:*** Humegon†; Menogon; Menopur; Merional; ***Denm.:*** Menogon†; Menopur; ***Fin.:*** Menogon†; Menopur; ***Fr.:*** Menopur; ***Ger.:*** Humegon†; Menogon; ***Gr.:*** Altermon; Menogon; Menopur; Merional; Pergogreen†; Pergonal†; ***Hong Kong:*** Menogon; Menopur; Merional; Pergonal; ***Hung.:*** Menogon†; Menopur; Merional; ***India:*** Eventin; Pergonal; Pregnorm; ***Irl.:*** Humegon; Menogon†; Menopur; ***Israel:*** Humegon†; Menogon; Menopur; Pergonal†; ***Ital.:*** Humegon†; Menogon; Meropur; ***Jpn:*** Gonadoryl; ***Malaysia:*** Menopur; ***Mex.:*** Humegon†; Merapur HP; Merional; Pergonal†; ***Neth.:*** Humegon; Menogon; Menopur; Pergonal†; ***Norw.:*** Menopur; ***Pol.:*** Menopur; ***Port.:*** Humegon†; ***Rus.:*** Menogon (Меногон); Menopur (Меопур); Pergonal (Пергонал); ***S.Afr.:*** Humegon†; Pergonal†; ***Singapore:*** Menogon; ***Spain:*** HMG; Menopur; Pergonal†; ***Swed.:*** Menopur; ***Switz.:*** Menogon†; Menopur; Merional; Pergonal†; ***Thai.:*** IVF-M; Menogon; ***Turk.:*** Menogon; Pergonal; ***UK:*** Menogon†; Menopur; Merional; ***USA:*** Humegon; Menopur; Pergonal†; Repronex; ***Venez.:*** Pergonal†.

Hydroxyestrone Diacetate

Hidroxiestrona, diacetato de; 16α-Hydroxyoestrone Diacetate. 3,16α-Dihydroxyestra-1,3,5(10)-trien-17-one diacetate.

$C_{22}H_{26}O_5$ = 370.4.

CAS — 566-76-7 (hydroxyestrone); 1247-71-8 (hydroxyestrone diacetate).



(hydroxyestrone)

Profile

Hydroxyestrone diacetate is an oestrogen (see Estradiol, p.2097). It has been given in vulvovaginal disorders and for female infertility.

Hydroxyprogesterone Caproate *(BANM, rINN)*

17-AHPC; Caproate d'hydroxyprogestirone; Caproato de hidroxiprogesterona; Hidroksiprogesteron Heksanoat; Hidroksiprogesteron Kaproat; Hydroxyprogesterone Hexanoate; Hydroxyprogesteroni Caproas; NSC-17592. 3,20-Dioxopregn-4-en-17α-yl hexanoate; 17α-Hydroxypregn-4-ene-3,20-dione hexanoate.

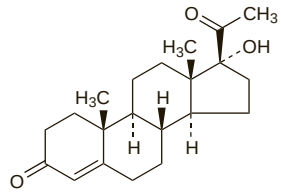
Гидроксипрогестерона Капроат

$C_{27}H_{40}O_4$ = 428.6.

CAS — 68-96-2 (hydroxyprogesterone); 630-56-8 (hydroxyprogesterone caproate).

ATC — G03DA03.

ATC Vet — QG03DA03.



(hydroxyprogesterone)

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

USP 31 (Hydroxyprogesterone Caproate). A white or creamy-white, crystalline powder. Odourless or having a slight odour. Insoluble in water; soluble in ether; slightly soluble in benzene. Protect from light. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125).

There may be local reactions at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may occur during or immediately after injection of hydroxyprogesterone caproate but can be avoided by injecting the drug very slowly.

Pregnancy. Abnormalities reported in infants born to mothers who had received hydroxyprogesterone during pregnancy have included tetralogy of Fallot in one infant,[1] genito-urinary abnormalities in 2 infants,[2] and adrenocortical carcinoma in one infant.[3]

1. Heinonen OP, *et al*. Cardiovascular birth defects and antenatal exposure to female sex hormones. *N Engl J Med* 1977; **296:** 67–70.
2. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; **224:** 315–19.
3. Mann JR, *et al*. Transplacental carcinogenesis (adrenocortical carcinoma) associated with hydroxyprogesterone hexanoate. *Lancet* 1983; **ii:** 580.

Interactions

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

Uses and Administration

Hydroxyprogesterone caproate is a progestogen structurally related to progesterone (p.2125) that has been used for recurrent miscarriage and various menstrual disorders. In recurrent miscarriage associated with proven progesterone deficiency, doses of 250 to 500 mg weekly by intramuscular injection have been given during the first half of pregnancy. Hydroxyprogesterone caproate has also been used to prevent premature labour (see below).

The acetate and the enantate have also been used.

Premature labour. In women who have a history of spontaneous premature delivery (p.2003), there is some evidence to suggest that prophylactic progesterone, may reduce the risk for premature delivery in subsequent pregnancies. A placebo-controlled study[1] has used intramuscular injections of hydroxyprogesterone caproate, starting in weeks 16 to 20 of gestation and continuing until delivery or week 36. The risk of delivery at less than 37 weeks was reduced in women given hydroxyprogesterone, but the rate was still high at 36.3% of 306 women compared with 54.9% of 153 given placebo. Vaginal progesterone has been found to reduce the frequency of uterine contractions and the rate of preterm delivery in women at high risk,[2] and to reduce preterm delivery in women with a short cervix at mid-gestation.[3] The best timing of therapy is unclear, although two retrospective analyses[4,5] found that rates of preterm delivery were similar for two groups of women started on hydroxyprogesterone prophylaxis at either 16 to 20.9 weeks of gestation or 21 to 26.9 weeks. Another retrospective study[6] suggested that early cessation of hydroxyprogesterone was associated with an increased risk of spontaneous recurrent preterm delivery and that treatment should continue until 36 weeks of gestation.

Systematic reviews[7,8] of studies using progestogens (mainly hydroxyprogesterone) have concluded that prophylaxis does reduce the risk of preterm delivery and low birth-weight (less than 2.5 kg). However, further study is required, particularly to identify the optimal timing, route, and dose of treatment, and long-term effects on infant health.[8] Based on limited data, an expert committee in the USA has recommended[9] that the use of progesterone and hydroxyprogesterone should be restricted to women with a history of previous spontaneous delivery at less than 37

weeks. In Canada,[10] a history of preterm labour is considered an indication for intramuscular hydroxyprogesterone caproate 250 mg weekly, or vaginal progesterone 100 mg daily, given from 20 weeks of gestation until the risk of prematurity is low. For women with a short cervix (less than 15 mm at 22 to 26 weeks of gestation), vaginal progesterone 200 mg daily may be used.

There is an increased risk of preterm delivery in twin gestations, but the use of hydroxyprogesterone does not appear to be of benefit.[11]

1. Meis PJ, *et al.* Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003; **348:** 2379–85.
2. da Fonseca EB, *et al.* Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2003; **188:** 419–24.
3. Fonseca EB, *et al.* Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med* 2007; **357:** 462–9.
4. González-Quintero VH, *et al.* Gestational age at initiation of 17α-hydroxyprogesterone caproate (17P) and recurrent preterm delivery. *J Matern Fetal Neonatal Med* 2007; **20:** 249–52.
5. How HY, *et al.* Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? *Am J Obstet Gynecol* 2007; **197:** 260.e1–4.
6. Rebarber A, *et al.* Increased recurrence of preterm delivery with early cessation of 17-alpha-hydroxyprogesterone caproate. *Am J Obstet Gynecol* 2007; **196:** 224.e1–4.
7. Sanchez-Ramos L, *et al.* Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. *Obstet Gynecol* 2005; **105:** 273–9.
8. Dodd JM, *et al.* Prenatal administration of progesterone for preventing preterm birth. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 27/06/08).
9. American College of Obstetrics and Gynecologist Committee on Obstetric Practice. Use of progesterone to reduce preterm birth (ACOG committee opinion number 291, issued November 2003). *Int J Gynecol Obstet* 2004; **84:** 93–4.
10. Farine D, *et al.* Society of Obstetricians and Gynaecologists of Canada. The use of progesterone for prevention of preterm birth. *J Obstet Gynaecol Can* 2008; **30:** 67–71. Also available at: http://www.sogc.org/guidelines/documents/guiJOGC202TU0801.pdf (accessed 27/06/08)
11. Rouse DJ, *et al.* A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007; **357:** 454–61.

Preparations

USP 31: Hydroxyprogesterone Caproate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Gestageno; Proluton Depot; ***Austria:*** Proluton Depot; ***Chile:*** Primolut Depot†; ***Cz.:*** Neolutin Forte; ***Fr.:*** Progesterone-retard Pharlon; ***Ger.:*** Progesteron-Depot; Proluton Depot; ***Gr.:*** Proluton Depot; ***India:*** Maintane; NT-Natal; Proluton Depot; ***Israel:*** Depolut†; Proluton Depot; ***Ital.:*** Lentogest; Proluton; ***Malaysia:*** Jenaprogon†; Proluton Depot; ***Mex.:*** Caposten; Primolut Depot; ***Neth.:*** Proluton Depot†; ***Philipp.:*** Proluton Depot; ***Pol.:*** Kaprogest; ***Singapore:*** Proluton Depot; ***Thai.:*** Proluton Depot; ***Turk.:*** Proluton Depo; ***USA:*** Hylutin†.

Multi-ingredient: ***Arg.:*** Dos Dias N; Primosiston; ***Braz.:*** Gestadinona; Trinestril; ***Chile:*** Gravidinona†; ***Ger.:*** Gravibinon†; Syngynon†; ***Ital.:*** Gravibinan†; ***Mex.:*** Gravidinona; Primosiston†; ***Switz.:*** Primosiston†; ***Venez.:*** Primosiston†.

Leuprorelin *(BAN, rINN)* ⊗

Leuprolide; Leuproreliini; Leuprorelina; Leuprorelinas; Leuproréline; Leuprorelinum. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

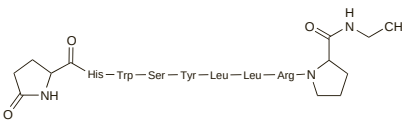
Лейпрорелин

$C_{59}H_{84}N_{16}O_{12}$ = 1209.4.

CAS — 53714-56-0.

ATC — L02AE02.

ATC Vet — QL02AE02.



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

Ph. Eur. 6.2 (Leuprorelin). A synthetic nonapeptide analogue of the hypothalamic peptide gonadorelin. It is obtained by chemical synthesis and is available as an acetate. A white or almost white, hygroscopic, powder. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Leuprorelin Acetate *(BANM, rINNM)* ⊗

Abbott-43818; Acetato de leuprorelina; Leuprolide Acetate *(USAN)*; Leuproreliiniasetaatti; Leuprorelinacetat; Leuproréline, Acétate de; Leuprorelini Acetas; Löprorelin Asetat; TAP-144.

Лейпрорелина Ацетат

$C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$ = 1269.5.

CAS — 74381-53-6.

ATC — L02AE02.

ATC Vet — QL02AE02.

Pharmacopoeias. In *US.*

USP 31 (Leuprolide Acetate). Store in airtight containers at a temperature not exceeding 30°.

Adverse Effects and Precautions

As for Gonadorelin, p.2106. Thrombocytopenia and leucopenia have been reported rarely.

Benign intracranial hypertension. Increased intracranial pressure associated with leuprorelin treatment has been reported in a few isolated cases.[1,2]

1. Arber N, *et al.* Pseudotumor cerebri associated with leuprorelin acetate. *Lancet* 1990; **335:** 668.
2. Boot JH. Pseudotumour cerebri as a side effect of leuprorelin acetate. *Ir J Med Sci* 1996; **165:** 60.

Effects on the eyes. Leuprorelin may be associated with blurred vision, usually lasting 1 to 2 hours after injection, but in rare instances longer.[1] Haemorrhage or occlusion of intra-ocular blood vessels, ocular pain, and lid oedema have also been reported but the association is less well established.

1. Fraunfelder FT, Edwards R. Possible ocular adverse effects associated with leuprolide injections. *JAMA* 1995; **273:** 773–4.

Hypersensitivity. An anaphylactic reaction started within 5 minutes of the injection of a leuprorelin depot formulation in a patient with prostate cancer.[1] Recurrent anaphylaxis developed in another patient given a depot injection of leuprorelin acetate for endometriosis, requiring both acute and chronic management.[2]

1. Taylor JD. Anaphylactic reaction to LHRH analogue, leuprorelin. *Med J Aust* 1994; **161:** 455.
2. Letterie GS, *et al.* Recurrent anaphylaxis to a depot form of GnRH analogue. *Obstet Gynecol* 1991; **78:** 943–6.

Local reactions. Local reactions, including erythema, pain, induration, granulomas, and sterile abscess are particularly associated with depot injections of gonadorelin analogues such as leuprorelin and triptorelin;[1-5] they may also occur with subcutaneous daily injection.[1] It has been suggested that the depot vehicle, a lactic acid-glycolic acid copolymer, may be responsible for many, although not all, such reactions.[1-5] Reactions are claimed to be more prevalent in children than in adults:[4] an incidence of about 5% of patients has been suggested. Reactions are apparently idiosyncratic and may occur at any time during therapy, may be intermittent, or may never recur.[4]

1. Manasco PK, *et al.* Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123:** 334–5.
2. Neely EK, *et al.* Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123:** 335.
3. Tonini G, *et al.* Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; **126:** 159.
4. Neely EK, *et al.* Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; **126:** 159–60.
5. Yasukawa K, *et al.* Leuprorelin acetate granulomas: case reports and review of the literature. *Br J Dermatol* 2005; **152:** 1045–7.

Pituitary apoplexy. Pituitary apoplexy occurred shortly after the injection of a depot formulation of leuprorelin for the treatment of prostate cancer in 2 patients with occult pituitary adenomas.[1,2] In a woman receiving leuprorelin daily in preparation for oocyte donation, symptoms began after the third dose.[3] Signs and symptoms in these cases included headache, visual disturbances, generalised weakness, nausea and vomiting, and haemorrhagic necrosis of the macroadenoma.

1. Morsi A, *et al.* Pituitary apoplexy after leuprolide administration for carcinoma of the prostate. *Clin Endocrinol (Oxf)* 1996; **44:** 121–4.
2. Reznik Y, *et al.* Pituitary apoplexy of a gonadotroph adenoma following gonadotrophin releasing hormone agonist therapy for prostatic cancer. *J Endocrinol Invest* 1997; **20:** 566–8.
3. Engel G, *et al.* Pituitary apoplexy after leuprolide injection for ovum donation. *J Adolesc Health* 2003; **32:** 89–93.

Interactions

As for Gonadorelin, p.2107.

Pharmacokinetics

Leuprorelin acetate is not active when given orally but is well absorbed on subcutaneous or intramuscular injection. After a parenteral dose it has an elimination half-life of about 3 hours.

◊ References.

1. Sennello LT, *et al.* Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. *J Pharm Sci* 1986; **75:** 158–60.
2. Periti P, *et al.* Clinical pharmacokinetics of depot leuprorelin. *Clin Pharmacokinet* 2002; **41:** 485–504.

Uses and Administration

Leuprorelin is an analogue of gonadorelin (p.2107) with similar properties. Continuous administration is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, in central precocious puberty, and in the management of endometriosis and uterine fibroids. It is also given before uterine surgery for endometrial reduction, and may be used in the treatment of breast cancer in premenopausal women. Leuprorelin is used as the acetate.

In the palliative treatment of **advanced prostate cancer**, leuprorelin acetate may be given by subcutaneous injection in a usual single daily dose of 1 mg. It is also given subcutaneously or intramuscularly as depot preparations but the dosage and route of these may differ between countries. In the USA, the dose is 7.5 mg monthly, 22.5 mg every 3 months, or 30 mg every 4 months, given subcutaneously or intramuscularly, depending on the preparation. A depot preparation of 45 mg given subcutaneously once every 6 months is also used. In the UK, leuprorelin acetate may also be used in advanced prostate cancer, as well as medical treatment of locally advanced cancer, as an adjuvant to surgery in locally advanced cancer at high risk of progression, or as an adjuvant to radiotherapy in high-risk localised or locally advanced disease. A dose of 3.75 mg may be given once a month, by subcutaneous or intramuscular injection, or 11.25 mg may be given subcutaneously every 3 months. A nonbiodegradable titanium alloy implant, which is inserted subcutaneously into the inner part of the upper arm, is also available in the USA for advanced disease. It contains 72 mg of leuprorelin acetate and delivers the drug at a controlled rate of 120 micrograms daily. After 12 months it must be removed, but can be replaced by another implant to continue therapy. An anti-androgen such as cyproterone acetate may be given for several days before beginning leuprorelin therapy and continued for about 3 weeks, to avoid the risk of a disease flare.

For the management of **endometriosis** and **uterine fibroids**, leuprorelin acetate 3.75 mg monthly may be given as a single depot injection, intramuscularly or subcutaneously. Alternatively, 11.25 mg may be given as an intramuscular depot every 3 months. Treatment is begun during the first 5 days of the menstrual cycle, and may be continued for up to 6 months for endometriosis, while in women with anaemia due to uterine fibroids it is continued, with iron supplementation, usually for up to 3 months. To prepare for uterine surgery including endometrial ablation or resection, a single 3.75 mg depot injection may be given 5 to 6 weeks before the procedure, or monthly for 3 to 4 months before surgery for uterine fibroids.

In the management of central **precocious puberty** leuprorelin acetate has been given by intramuscular depot injection in a dose of 300 micrograms/kg every 4 weeks, adjusted according to response. Doses of 50 micrograms/kg daily by subcutaneous injection, adjusted according to response, have also been used.

Leuprorelin acetate has also been given in other sex-hormone-related disorders.

◊ General references.

1. Plosker GL, Brogden RN. Leuprorelin: a review of its pharmacology and therapeutic use in prostatic cancer, endometriosis and other sex hormone-related disorders. *Drugs* 1994; **48:** 930–67.

Benign prostatic hyperplasia. For a discussion of the management of benign prostatic hyperplasia, including mention of the use of gonadorelin analogues and the view that they are unsatisfactory for indefinite therapy, see p.2178.

References to the use of leuprorelin.

1. Gabrilove JL, *et al.* Effect of long-acting gonadotropin-releasing hormone analog (leuprolide) therapy on prostatic size and symptoms in 15 men with benign prostatic hypertrophy. *J Clin Endocrinol Metab* 1989; **69:** 629–32.
2. Eri LM, Tveter KJ. A prospective, placebo-controlled study of the luteinizing hormone-releasing hormone agonist leuprolide as treatment for patients with benign prostatic hyperplasia. *J Urol (Baltimore)* 1993; **150:** 359–64.
3. Eri LM, Tveter KJ. Safety, side effects and patient acceptance of the luteinizing hormone releasing hormone agonist leuprolide in treatment of benign prostatic hyperplasia. *J Urol (Baltimore)* 1994; **152:** 448–52.
4. Eri LM, *et al.* Effects on the endocrine system of long-term treatment with the luteinizing hormone-releasing hormone agonist leuprolide in patients with benign prostatic hyperplasia. *Scand J Clin Lab Invest* 1996; **56:** 319–25.

Disturbed behaviour. Leuprorelin has been used in the treatment of men with paraphilias (p.954). Case series have reported reductions in abnormal sexual thoughts and behaviours.[1-3]

1. Briken P, *et al.* Treatment of paraphilia with luteinizing hormone-releasing hormone agonists. *J Sex Marital Ther* 2001; **27:** 45–55.