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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.
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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.
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4. Scialli AR, Levi AJ. Intermittent leuprolide acetate for the nonsurgical management of women with leiomyomata uteri. *Fertil Steril* 2000; **74:** 540–6.
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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.
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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.