Polycystic ovary syndrome. Gonadorelin and its analogues have been used in the management of infertility associated with polycystic ovary syndrome (see Infertility, p.2080), even though some product information contra-indicates their use in this syndrome.

Pulsatile gonadorelin has been tried for ovulation induction but rates of ovulation and pregnancy are poor when it is used alone in women with polycystic ovary syndrome. Pretreatment with a gonadorelin analogue for pituitary desensitisation before starting pulsatile gonadorelin has shown some benefit in patients with polycystic ovary syndrome who have high levels of luteinising hormone.[1] However, there is only limited clinical data from small short-term trials and case series on the use of pulsatile gonadorelin in these women.[2]

Gonadorelin analogues may be used for pituitary desensitisation before the use of gonadotrophins for ovulation induction, and there is a suggestion that this strategy may improve pregnancy rates compared with gonadotrophins alone in women with polycystic ovary syndrome.[3] Gonadorelin analogues are used also in ovarian stimulation protocols for assisted reproduction techniques.[1]

Women with polycystic ovary syndrome are at increased risk of ovarian hyperstimulation syndrome and must be carefully monitored throughout the use of ovulation induction regimens.[1]

1. Buckett WM, Tan SL. Use of luteinizing hormone releasing hormone agonists in polycystic ovary syndrome. *Baillieres Clin Obstet Gynaecol* 1998; **12:** 593–606.
2. Bayram N, *et al.* Pulsatile gonadotrophin releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 15/09/05).
3. 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 15/09/05).

Porphyria. For mention of the use of gonadorelin analogues to suppress cyclic premenstrual exacerbations of acute porphyria, see Buserelin, p.2084, Nafarelin, p.2118, and Triptorelin, p.2136.

Premenstrual syndrome. In women in whom other drug treatments for premenstrual syndrome (p.2099) are ineffective, use of a gonadorelin analogue, usually with HRT as 'add-back' therapy to prevent menopausal symptoms, may be considered.[1] Short-term therapy (3 months) has been used to confirm the diagnosis of premenstrual syndrome, or to predict the response to bilateral oophorectomy when this is being considered. Some references to the use of gonadorelin analogues in premenstrual syndrome are given below.[2-7]

1. Wyatt KM, *et al.* The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. *Br J Obstet Gynaecol* 2004; **111:** 585–93.
2. Hussain SY, *et al.* Buserelin in premenstrual syndrome. *Gynecol Endocrinol* 1992; **6:** 57–64.
3. Mezrow G, *et al.* Depot leuprolide acetate with estrogen and progestin add-back for long-term treatment of premenstrual syndrome. *Fertil Steril* 1994; **62:** 932–7.
4. Brown CS, *et al.* Efficacy of depot leuprolide in premenstrual syndrome: effect of symptom severity and type in a controlled trial. *Obstet Gynecol* 1994; **84:** 779–86.
5. West CP, Hillier H. Ovarian suppression with the gonadotrophin-releasing hormone agonist goserelin (Zoladex) in management of the premenstrual tension syndrome. *Hum Reprod* 1994; **9:** 1058–63.
6. Leather AT, *et al.* The treatment of severe premenstrual syndrome with goserelin with and without 'add-back' estrogen therapy: a placebo-controlled study. *Gynecol Endocrinol* 1999; **13:** 48–55.
7. Di Carlo C, *et al.* Use of leuprolide acetate plus tibolone in the treatment of severe premenstrual syndrome. *Fertil Steril* 2001; **75:** 380–4.

Preparations

USP 31: Gonadorelin for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Luteoliberina; ***Austria:*** Kryptocur; Lutrelef; Relefact LH-RH; ***Belg.:*** HRF; ***Braz.:*** Parlib†; ***Canad.:*** Lutrepulse; ***Cz.:*** Relefact LH-RH†; ***Fr.:*** Lutrelef; Stimu-LH; ***Ger.:*** Kryptocur; Lutrelef; Relefact LH-RH; ***Gr.:*** Relefact LH-RH; ***Hong Kong:*** Relisorm L†; ***Hung.:*** Relisorm I†; ***Irl.:*** HRF; ***Israel:*** Lutrelef†; Relefact LH-RH; ***Ital.:*** Kryptocur; Lutrelef; ***Neth.:*** Cryptocur; HRF; Lutrelef; Relefact LH-RH; ***NZ:*** HRF†; ***S.Afr.:*** HRF; ***Spain:*** Luforan†; ***Swed.:*** Lutrelef; ***Switz.:*** Kryptocur; Lutrelef; Relisorm L†; ***UK:*** HRF; ***USA:*** Factrel.

Goserelin *(BAN, USAN, rINN)* ⊗

Goserelíini; Goserelina; Goserelinas; Goséréline; Goserelinum; Goszerelin; ICI-118630. 3-[5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-(3-*O*-*tert*-butyl)-D-seryl-L-leucyl-L-arginyl-L-prolyl]carbazamide.

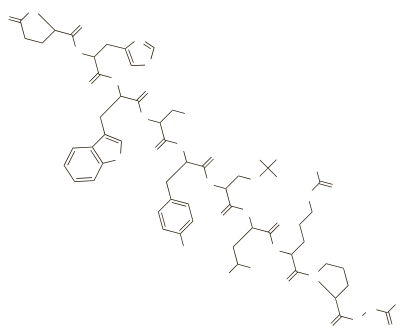
Гозерелин

$C_{59}H_{84}N_{18}O_{14}$ = 1269.4.

CAS — 65807-02-5.

ATC — L02AE03.

ATC Vet — QL02AE03.



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

Ph. Eur. 6.2 (Goserelin). A nonapeptide analogue of the hypothalamic decapeptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate. A white or almost white powder. Soluble in water; freely soluble in glacial acetic acid. It dissolves in dilute solutions of mineral acids and alkali hydroxides. Store at 2° to 8° in airtight containers. Protect from light.

Goserelin Acetate *(BANM, rINNM)* ⊗

Acetato de goserelina; Gosséréline, Acétate de; Goserelini Acetas; D-Ser (Bu^t)^6 Azgly^{10}-LHRH Acetate.

Гозерелина Ацетат

$C_{59}H_{84}N_{18}O_{14}$, $C_2H_4O_2$ = 1329.5.

CAS — 145781-92-6.

ATC — L02AE03.

ATC Vet — QL02AE03.

Adverse Effects and Precautions

As for Gonadorelin, p.2106. Some women may have vaginal bleeding during initial therapy, which normally resolves spontaneously.

Pituitary apoplexy. Pituitary apoplexy (a clinical syndrome caused by haemorrhage and infarction of a pituitary adenoma) occurred in a few elderly patients with a symptomless pituitary adenoma who were given goserelin for advanced prostate cancer.[1,2] Symptoms included headache, vomiting, visual disturbances, gradual impairment of consciousness, intermittent fever, and progressive hyponatraemia. Symptoms were treated with corticosteroid replacement therapy.

1. Ando S, *et al.* Pituitary apoplexy after goserelin. *Lancet* 1995; **345:** 458.
2. Eaton HJ, *et al.* Rapid onset of pituitary apoplexy after goserelin implant for prostate cancer: need for heightened awareness. *Intern Med J* 2001; **31:** 313–14.

Pharmacokinetics

Goserelin is almost completely absorbed after subcutaneous injection, and has a serum elimination half-life of 2 to 4 hours, which may be increased in renal impairment. More than 90% of a dose is excreted in urine, as unchanged drug and metabolites.

◊ Reviews.

1. Cockshott ID. Clinical pharmacokinetics of goserelin. *Clin Pharmacokinet* 2000; **39:** 27–48.

Uses and Administration

Goserelin is an analogue of gonadorelin (p.2107) with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, in breast cancer in pre- and peri-menopausal women, and in the management of endometriosis and uterine fibroids. It is also given before surgery for endometrial reduction and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility. Goserelin is usually given as the acetate but doses are expressed in terms of the base; 10.5 mg of goserelin acetate is equivalent to about 10 mg of goserelin.

Goserelin acetate is available as depot preparations; with one such preparation a dose equivalent to 3.6 mg of goserelin injected subcutaneously into the anterior abdominal wall provides effective suppression of oestradiol or testosterone for 28 days. A full response should be achieved by the end of this period and treatment is continued with repeated doses at 28-day intervals; in endometriosis, therapy is given for up to 6 months, while in women with anaemia as a result of uterine fibroids it is continued, with iron supplementation, for up to 3 months before surgery. In men with prostate cancer, preparations supplying the equivalent of 10.8 mg of goserelin, given every 12 weeks, may also be used.

In the treatment of prostatic cancer an anti-androgen such as cyproterone acetate may be given for several days before beginning goserelin therapy and continued for at least 3 weeks, to avoid the risk of a disease flare.

Regimens for oocyte collection for IVF use gonadorelin analogues for pituitary desensitisation before ovulation induction with gonadotrophins. The equivalent of 3.6 mg of goserelin is given as a subcutaneous depot injection and serum-oestradiol concentrations monitored until they decline to levels similar to those in the early follicular phase, a process which usually takes 7 to 21 days. Once downregulation occurs gonadotrophin (follicle stimulating) therapy is begun until an appropriate stage of follicular development, when it is withdrawn and chorionic gonadotrophin is given to induce ovulation.

Goserelin has also been given in other sex-hormone-related conditions.

◊ Reviews of goserelin.

1. Chrisp P, Goa KL. Goserelin: a review of its pharmacodynamic and pharmacokinetic properties, and clinical use in sex hormone-related conditions. *Drugs* 1991; **41:** 254–88.
2. Perry CM, Brogden RN. Goserelin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in benign gynaecological disorders. *Drugs* 1996; **51:** 319–46.

Endometriosis. Gonadorelin analogues such as goserelin 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' therapy, with concomitant hormone replacement, may be given in an attempt to reduce bone mineral density loss and vasomotor symptoms in women receiving goserelin.

References.

1. Shaw RW, *et al.* An open randomized comparative study of the effect of goserelin depot and danazol in the treatment of endometriosis. *Fertil Steril* 1992; **58:** 265–72.
2. Schlaff WD. Extending the treatment boundaries: Zoladex and add-back. *Int J Gynaecol Obstet* 1999; **64** (suppl 1): S25–S31.
3. Franke HR, *et al.* Gonadotropin-releasing hormone agonist plus "add-back" hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. *Fertil Steril* 2000; **74:** 534–9.
4. Pierce SJ, *et al.* Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. *Fertil Steril* 2000; **74:** 964–8.

Fibroids. Gonadorelin analogues such as goserelin have been tried as an adjunct or an alternative to surgery in the treatment of uterine fibroids (p.2107) although there has been some concern that this might complicate the diagnosis of malignancy. Some further references are listed below.

1. Lumsden MA, *et al.* Treatment with the gonadotrophin releasing hormone-agonist goserelin before hysterectomy for uterine fibroids. *Br J Obstet Gynaecol* 1994; **101:** 438–42.
2. Benagiano G, *et al.* Zoladex (goserelin acetate) and the anemic patient: results of a multicenter fibroid study. *Fertil Steril* 1996; **66:** 223–9.
3. Parazzini F, *et al.* Goserelin acetate to avoid hysterectomy in premenopausal women with fibroids requiring surgery. *Eur J Obstet Gynecol Reprod Biol* 1999; **87:** 31–3.

Malignant neoplasms. Goserelin is effective in the treatment of prostate cancer (p.671). It has produced a response similar to that of orchidectomy (surgical removal of the testes) in patients with metastatic prostate cancer.[1] Goserelin has been combined with an anti-androgen such as flutamide to provide maximum androgen blockade, but this appears to produce modest additional benefits at most. There is some evidence that adjuvant therapy with goserelin may improve survival in patients with localised or locally advanced prostate cancer when combined with radiotherapy or radical prostatectomy, and adjuvant use of goserelin appears to be more beneficial than neoadjuvant use.[2]

Goserelin may also be used as hormonal therapy in premenopausal women with advanced breast cancer (p.661); it seems to be as effective as oophorectomy,[3] and use with tamoxifen is more effective than goserelin alone.[4] It is also used as an alternative or addition to adjuvant chemotherapy in pre- or peri-menopausal women with oestrogen-receptor positive early breast cancer.[5-9]

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. Correction. *ibid.* 2005; **143:** 764–5.