Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Depostat; ***Ger.:*** Depostat†; ***Ital.:*** Depostat†; ***Mex.:*** Primostat; ***Rus.:*** Depostat (Депостат); ***Spain:*** Depostat†; ***Switz.:*** Depostat†.

Gestrinone *(BAN, USAN, rINN)* ⊗

A-46745; Ethylnorgestrienone; Gestrinon; Gestrinona; Gestrinoni; Gestrinonum; R-2323; RU-2323. 13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,9,11-trien-20-yn-3-one.

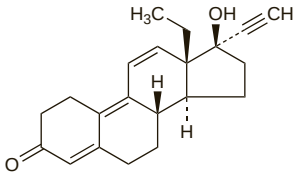
Гестринон

$C_{21}H_{24}O_2$ = 308.4.

CAS — 16320-04-0; 40542-65-2.

ATC — G03XA02.

ATC Vet — QG03XA02.



Adverse Effects and Precautions

As for Danazol, p.2090.

Interactions

Antiepileptic drugs and rifampicin may accelerate the metabolism of gestrinone.

Pharmacokinetics

Gestrinone is well absorbed after oral doses with negligible first-pass hepatic metabolism. Peak plasma concentrations occur about 3 hours after a dose. The plasma half-life is about 24 hours. Gestrinone is metabolised in the liver to form conjugated metabolites.

Uses and Administration

Gestrinone is a synthetic steroidal hormone reported to have antiprogestogenic properties, with some androgenic and anti-oestrogenic activity; it inhibits pituitary gonadotrophin release. It is used in the treatment of endometriosis (p.2091) in oral doses of 2.5 mg twice weekly; the first dose is taken on the first day of the menstrual cycle with the second dose taken three days later; thereafter the doses should be taken on the same two days of each week, usually for a period of 6 months. If a dose is missed it should be given as soon as possible and the original dose sequence maintained thereafter; if 2 or more doses are missed gestrinone should be stopped and restarted on the first day of a new cycle after a negative pregnancy test.

Gestrinone has been studied in the management of cyclical mastalgia (p.2092) and uterine fibroids (p.2107).

◊ References.

1. Thomas EJ, Cooke ID. Impact of gestrinone on the course of asymptomatic endometriosis. *BMJ* 1987; **294:** 272–4.
2. Brosens IA, *et al.* The morphologic effect of short-term medical therapy of endometriosis. *Am J Obstet Gynecol* 1987; **157:** 1215–21.
3. Coutinho EM, Azadian-Boulanger G. Treatment of endometriosis by vaginal administration of gestrinone. *Fertil Steril* 1988; **49:** 418–22.
4. Hornstein MD, *et al.* A randomized double-blind prospective trial of two doses of gestrinone in the treatment of endometriosis. *Fertil Steril* 1990; **53:** 237–41.
5. Peters F. Multicentre study of gestrinone in cyclical breast pain. *Lancet* 1992; **339:** 205–8.
6. Worthington M, *et al.* A randomized comparative study of the metabolic effects of two regimens of gestrinone in the treatment of endometriosis. *Fertil Steril* 1993; **59:** 522–6.
7. Gestrinone Italian Study Group. Gestrinone versus a gonadotropin-releasing hormone agonist for the treatment of pelvic pain associated with endometriosis: a multicenter, randomized, double-blind study. *Fertil Steril* 1996; **66:** 911–19.
8. Dawood MY, *et al.* Clinical, endocrine, and metabolic effects of two doses of gestrinone in treatment of pelvic endometriosis. *Am J Obstet Gynecol* 1997; **176:** 387–94.
9. La Marca A, *et al.* Gestrinone in the treatment of uterine leiomyomata: effects on uterine blood supply. *Fertil Steril* 2004; **82:** 1694–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nemestran; ***Austral.:*** Dimetriose; ***Braz.:*** Dimetrose; ***Cz.:*** Nemestran†; ***Ital.:*** Dimetrose; ***Malaysia:*** Dimetriose; ***Mex.:*** Nemestran; ***Neth.:*** Nemestran; ***NZ:*** Dimetriose; ***Port.:*** Dimetriose; ***S.Afr.:*** Tridomose; ***Singapore:*** Dimetriose; ***Spain:*** Nemestran†; ***Switz.:*** Nemestran; ***Thai.:*** Dimetriose; ***UK:*** Dimetriose.

Gonadorelin *(BAN, rINN)* ⊗

Follicle Stimulating Hormone-releasing Factor; GnRH; Gonadoliberin; Gonadoreliini; Gonadorelina; Gonadoréline; Gonadorelinum; Gonadotrophin-releasing Hormone; Hoe-471; LH/FSH-RF; LH/FSH-RH; LH-RF; LH-RH; Luliberin; Luteinising Hormone-releasing Factor. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosylglycyl-L-leucyl-L-arginyl-L-prolylglycinamide.

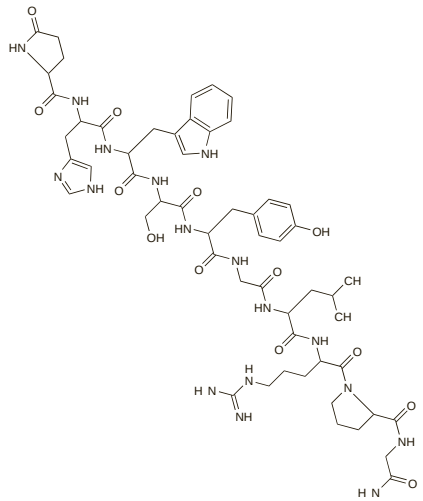
Гонадорелин

$C_{55}H_{75}N_{17}O_{13}$ = 1182.3.

CAS — 33515-09-2.

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.



Gonadorelin Acetate *(BANM, USAN, rINNM)* ⊗

Abbott-41070; Acetato de gonadorelina; Gonadolrelin-acetát; Gonadoreliniasetaatti; Gonadorelinacetat; Gonadorelin-acetát; Gonadoréline, acétate de; Gonadorelini acetas; Gonadorelino acetatas.

Гонадорелина Ацетат

$C_{55}H_{75}N_{17}O_{13}.xC_2H_4O_2.yH_2O$.

CAS — 34973-08-5 (anhydrous gonadorelin diacetate); 52699-48-6 (gonadorelin diacetate tetrahydrate).

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US* for veterinary use only.

USP 31 (Gonadorelin Acetate). A white to slightly yellowish powder. Soluble in water; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature of not more than 8°.

Ph. Eur. 6.2 (Gonadorelin Acetate). The acetate form of a hypothalamic peptide that stimulates the release of follicle-stimulating hormone and luteinising hormone from the pituitary gland. It is obtained by chemical synthesis. A white or slightly yellowish powder; soluble in water and in 1% v/v glacial acetic acid; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Gonadorelin Hydrochloride *(BANM, USAN, rINNM)* ⊗

AY-24031; Gonadoréline, Chlorhydrate de; Gonadorelini Hydrochloridum; Hidrocloruro de gonadorelina.

Гонадорелина Гидрохлорид

$C_{55}H_{75}N_{17}O_{13}.2HCl$ = 1255.2.

CAS — 51952-41-1.

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

Pharmacopoeias. In *US.*

USP 31 (Gonadorelin Hydrochloride). A synthetic polypeptide hormone having the property of stimulating the release of the luteinising hormone from the hypothalamus. It is extremely hygroscopic. Protect from exposure to moisture and store in airtight well-sealed containers, in a desiccator.

Adverse Effects

Gonadorelin and its analogues are generally well tolerated but may cause gastrointestinal adverse effects, usually nausea and abdominal pain or discomfort. There may be headache or lightheadedness, and an increase in menstrual bleeding. Continued therapy with gonadorelin analogues results in paradoxical suppression of the pituitary gonadal axis; in premenopausal women this may produce menopausal symptoms, including vaginal dryness, hot flushes, and loss of libido. If sufficiently prolonged the suppression of circulating oestrogens may lead to osteoporosis. In men, hot flushes and sexual dysfunction can occur, and breast swelling and tenderness have been reported infrequently with gonadorelin analogues. Long-term treatment can also cause a loss of bone mineral density in men. Other adverse effects reportedly associated with gonadorelin analogue therapy, and presumably related to changes in the hormonal milieu, include mood changes, nervousness, palpitations, acne and dry skin, changes in scalp and body hair, alterations in liver function tests and blood lipids, and decreased glucose tolerance. Arthralgia and paraesthesias have been reported. Ovarian hyperstimulation (as seen with chorionic gonadotrophin, p.2085), although rare, has occurred in women given gonadorelin.

Reactions or pain may occur at the site of injection with rash (local or generalised), thrombophlebitis, swelling, or pruritus. Hypersensitivity reactions, including bronchospasm and anaphylaxis, have been reported.

Other effects may be a consequence of the particular use of gonadorelin or its analogues. Tumour flare, due to an initial surge in testosterone concentrations, has been reported in the initial stages of treatment for cancer of the prostate and prophylactic anti-androgen therapy may be added. Flare may manifest as an increase in bone pain; occasionally there has been spinal cord compression, or a worsening of urinary-tract symptoms with haematuria and urinary obstruction. Acute degeneration of submucous fibroids with severe bleeding has been reported following use of leuprorelin. An initial increase in signs and symptoms has also been reported in women with breast cancer receiving gonadorelin analogues; hypercalcaemia has occurred in those with metastatic disease. In girls being treated for precocious puberty, vaginal bleeding may occur in the first month of treatment because of initial ovarian stimulation followed by treatment-induced oestrogen withdrawal.

Hypersensitivity. Acquired hypersensitivity led to an anaphylactic reaction after an intravenous dose of gonadorelin in a man who had been receiving pulsatile subcutaneous gonadorelin therapy for 10 weeks.[1]

1. Potashnik G, *et al.* Anaphylactic reaction to gonadotropin-releasing hormone. *N Engl J Med* 1993; **328:** 815.

Osteoporosis. Long-term use of a gonadorelin analogue results in oestrogen deficiency-associated osteoporosis and various drugs have been investigated for their ability to reduce this effect. Parathyroid hormone has been reported to prevent bone loss in small studies of young women receiving nafarelin.[1,2] 'Add-back' therapy with tibolone[3,4] or oestrogen plus progestogen[5,6] has also had beneficial effects on bone mineral density in women receiving gonadorelin analogues. However, studies have used various combination regimens and it is not possible to determine which is most effective.[6,7] There is less information available about the management of osteoporosis in men receiving gonadorelin analogues as androgen deprivation therapy, but measures have included supplemental calcium and vitamin D, and the use of bisphosphonates.[8] Raloxifene is also under investigation in both women[9] and men.[10]

1. Finkelstein JS, *et al.* Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; **331:** 1618–23.
2. Finkelstein JS, *et al.* Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA* 1998; **280:** 1067–73.
3. Lindsay PC, *et al.* The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). *Fertil Steril* 1996; **65:** 342–8.
4. Palomba S, *et al.* A clinical trial of the effects of tibolone administered with gonadorelin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertil Steril* 1998; **70:** 111–18.
5. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.

6. Sagsveen M, *et al.* Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 15/09/05).
7. Surrey ES, the Add-back Consensus Working Group. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? *Fertil Steril* 1999; **71:** 420–4.
8. Smith MR. Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. *Cancer* 2003; **97** (suppl): 789–95.
9. Palomba S, *et al.* Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. *J Clin Endocrinol Metab* 2002; **87:** 4476–81.
10. Smith MR, *et al.* Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3841–6.

Pituitary apoplexy. Pituitary apoplexy has been reported after endocrine stimulation testing using gonadorelin. A review[1] of 14 cases found that 2 patients had received gonadorelin alone but most had also received protirelin (thyrotropin-releasing hormone). The onset of initial symptoms was within 2 hours and pituitary tumour haemorrhage was much more common than infarction alone.

1. Matsuura I, *et al.* Infarction followed by hemorrhage in pituitary adenoma due to endocrine stimulation test. *Endocr J* 2001; **48:** 493–8.

Precautions

Gonadorelin or its analogues should not generally be used in patients with pituitary adenoma as haemorrhagic infarction (pituitary apoplexy) has sometimes occurred. It has also been recommended that patients with weight-related amenorrhoea should not receive these drugs until their weight is corrected. Although at least one manufacturer recommends that gonadorelin should not be used in women with polycystic ovary disease or with endometriotic cysts, gonadorelin and its analogues have been used for ovulation induction in polycystic disease and produced improvement in uterine fibroids; gonadorelin analogues have also been used with benefit in endometriosis. Gonadorelin analogues may increase cervical resistance, making it difficult to dilate the cervix for intra-uterine surgical procedures. Gonadorelin or its analogues should be stopped if the patient becomes pregnant. Contraceptive measures should be taken to protect against unwanted ovulation. Men at risk from tumour flare should be carefully monitored in the first month of therapy.

Interactions

Drugs affecting pituitary secretion of gonadotrophins may alter the response to gonadorelin or its analogues; other hormonal therapy and corticosteroids can affect the response. Spironolactone and levodopa can stimulate gonadotrophins while phenothiazines, dopamine antagonists, digoxin, and sex hormones can inhibit gonadotrophin secretion.

Pharmacokinetics

Gonadorelin is poorly absorbed from the gastrointestinal tract. It has a terminal plasma half-life of only 10 to 40 minutes after intravenous injection. It is hydrolysed in the plasma and excreted in the urine as inactive metabolites.

Gonadorelin analogues are absorbed after oral, intramuscular, intranasal, or rectal doses and have a longer half-life.

Uses and Administration

Gonadorelin is a synthetic form of hypothalamic gonadotrophin-releasing hormone. It stimulates the synthesis and release of follicle-stimulating hormone and, in particular, luteinising hormone in the anterior lobe of the pituitary. The secretion of endogenous gonadotrophin-releasing hormone is pulsatile and is controlled by several factors including circulating sex hormones. Gonadotrophic hormones (gonadotrophins), released from the pituitary gland in response to gonadorelin, stimulate secretion of sex hormones from the gonads. A single dose of gonadorelin or one of its analogues has the effect of increasing circulating sex hormones; continued use leads to down-regulation of gonadorelin-receptor synthesis in the pituitary and results in a paradoxical reduction in sex-hormone secretion.

Gonadorelin may be given as the base, acetate, or hydrochloride, and the dose may be expressed in terms of any of these.

Gonadorelin is used in the **diagnosis of hypothalamic-pituitary-gonadal dysfunction**. Assessment is usually based on the response to a dose of gonadorelin of 100 micrograms by intravenous or subcutaneous injection. In females, where possible, it should be given early in the follicular stage of the menstrual cycle. In the UK, the *BNFC* includes a single dose of 2.5 micrograms/kg, to a maximum of 100 micrograms, for children from the age of 1 year.

Gonadorelin is also used in the treatment of **amenorrhoea** and **infertility** associated with hypogonadotrophic hypogonadism. Weight-related amenorrhoea should have been corrected by diet. Treatment in such conditions is based on an intermittent pulse pump providing 5 to 20 micrograms over one minute every 90 minutes, either subcutaneously or intravenously, for up to 6 months or until conception.

Gonadorelin or, more usually, its analogues such as buserelin, goserelin, leuprorelin, nafarelin, and triptorelin (which are more potent and have a longer duration of action) are used in cryptorchidism, malignant neoplasms (especially of the prostate), and in delayed and precocious puberty.

Benign prostatic hyperplasia. The gonadorelin analogues have been tried in the management of benign prostatic hyperplasia (p.2178) but are considered unsatisfactory for indefinite use. See also under Leuprorelin Acetate, p.2111, and Nafarelin Acetate, p.2118.

Cryptorchidism. Although surgery remains the treatment with the best success rate, primary hormonal therapy with gonadorelin or an analogue is widely used for cryptorchidism (p.2079). Systematic reviews[1,2] suggest a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, a predictor of future fertility.[3]

1. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80:** 2795–9.
2. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20:** 357–9.
3. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (issued March 2008). Available at: http://www.uroweb.org/fileadmin/user_upload/Guidelines/Paediatric%20Urology.pdf (accessed 31/03/08)

Delayed and precocious puberty. For mention of the use of gonadorelin or its analogues in delayed and precocious puberty, see p.2079 and p.2081 respectively. Benefit in delayed puberty is most likely in those cases where it is secondary to hypogonadism (see p.2079).

Diagnosis of hypothalamic and pituitary dysfunction. Gonadorelin may be used in the diagnosis of hypothalamic-pituitary-gonadal dysfunction such as in hypogonadism, delayed puberty, and precocious puberty.[1,2]

1. Eckert KL, *et al.* A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. *Pediatrics* 1996; **97:** 517–19.
2. De Martino MU, *et al.* Dynamic testing in the evaluation of male gonadal function. *J Endocrinol Invest* 2003; **26** (suppl): 107–13.

Disturbed behaviour. Gonadorelin analogues such as leuprorelin (p.2111) or triptorelin (p.2136) may be tried in men with paraphilias.

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' therapy (hormone replacement) may be given in an attempt to reduce bone mineral density loss and vasomotor symptoms.

Some references to gonadorelin analogues in endometriosis are listed below. For further references, see Buserelin Acetate, p.2083, Goserelin Acetate, p.2108, Leuprorelin Acetate, p.2112, and Nafarelin Acetate, p.2118.

1. Gargiulo AR, Hornstein MD. The role of GnRH agonists plus add-back therapy in the treatment of endometriosis. *Semin Reprod Endocrinol* 1997; **15:** 273–84.
2. Hemmings R. Combined treatment of endometriosis: GnRH agonists and laparoscopic surgery. *J Reprod Med* 1998; **43** (suppl 3): 316–20.
3. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.
4. Surrey ES. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? *Fertil Steril* 1999; **71:** 420–4.

Fibroids. Uterine fibroids (leiomyomas) are benign tumours of uterine smooth muscle.[1,2] They are found in about 25% of women, most of whom are aged in their 30s or 40s when the condition becomes symptomatic. Fibroids may give rise to menstrual problems, particularly menorrhagia, pelvic discomfort, infertility, and miscarriage. Although small fibroids may not require treatment, the management of symptomatic fibroids has traditionally been surgical. However, because fibroids are oestrogen responsive, gonadorelin analogues have also been tried as medical treatment for their ability to induce a hypogonadotrophic hypogonadal state. These drugs produce a significant reduction in uterine and fibroid volume, and amenorrhoea, but when treatment stops uterine and fibroid volume tend to return to pretreatment values. The hypoestrogenism produced during treatment also causes menopausal symptoms such as hot flushes and vaginal dryness, and bone loss may occur. Giving oestrogens or progestogens, once the uterine fibroid size has significantly reduced, has been tried as 'add-back' therapy to counteract these adverse effects.[3,4] Tibolone has also been reported to reduce bone loss and vasomotor symptoms.[2] Subcutaneous injection of long-acting depot preparations of gonadorelin or its analogues appears to be the preferred method and is considered a valuable pre-operative adjunct to surgery, simplifying the procedure by reducing uterine and fibroid volume and intra-operative blood loss, as well as correcting pre-operative iron-deficiency anaemia.[5,6] However, concern has been expressed that the use of gonadorelin analogues for treating fibroids may complicate the differentiation of benign and malignant growths.[7]

For further references to use of gonadorelin analogues in the treatment of fibroids, see Buserelin Acetate, p.2083, Goserelin Acetate, p.2108, Leuprorelin Acetate, p.2112, Nafarelin Acetate, p.2118, and Triptorelin, p.2136.

Other drugs that are under investigation for fibroids include gonadorelin antagonists such as cetrorelix and ganirelix, and mifepristone. Danazol and gestrinone have also been tried in a small number of patients.[2]

1. Stewart EA. Uterine fibroids. *Lancet* 2001; **357:** 293–8.
2. De Leo V, *et al.* A benefit-risk assessment of medical treatment for uterine leiomyomas. *Drug Safety* 2002; **25:** 759–79.
3. Friedman AJ, *et al.* Efficacy and safety considerations in women with uterine leiomyomas treated with gonadotropin-releasing hormone agonists: the estrogen threshold hypothesis. *Am J Obstet Gynecol* 1990; **163:** 1114–19.
4. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.
5. Lethaby A, *et al.* Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 15/09/05).
6. Agence Française de Sécurité Sanitaire des Produits de Santé. Les traitements médicamenteux du fibrome utérin - octobre 2004. Available at: http://afssaps.sante.fr/pdf/5/rbp/fibrorec.pdf (accessed 15/09/05)
7. Mesia AF, *et al.* Aborted leiomyosarcoma after treatment with leuprolide acetate. *Obstet Gynecol* 1998; **92:** 664–6.

Growth retardation. The use of a gonadorelin analogue to delay precocious puberty may improve the final height of children with the disorder. However, the use of a gonadorelin analogue with growth hormone in short but otherwise normal children is controversial—see under Triptorelin, p.2136.

Hirsutism. For reference to the use of gonadorelin analogues such as leuprorelin in the treatment of hirsutism, see p.2112.

Infertility. Gonadorelin and its analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both women and men (p.2080). Some further references are given below. See also under Buserelin Acetate, p.2083, Leuprorelin Acetate, p.2112, and Nafarelin Acetate, p.2118.

For mention of the use of gonadorelin and its analogues in the management of infertility in polycystic ovary syndrome, see below.

1. Lingle L, Hart LL. Gonadotropin-releasing hormone in infertility. *DICP Ann Pharmacother* 1989; **23:** 246–8.
2. Thomas AK, *et al.* Induction of ovulation with subcutaneous pulsatile gonadotropin-releasing hormone: correlation with body weight and other parameters. *Fertil Steril* 1989; **51:** 786–90.
3. Homburg R, *et al.* One hundred pregnancies after treatment with pulsatile luteinising hormone releasing hormone to induce ovulation. *BMJ* 1989; **298:** 809–12.
4. Kovacs GT, *et al.* Induction of ovulation with gonadotrophin-releasing hormone—life-table analysis of 50 courses of treatment. *Med J Aust* 1989; **151:** 21–6.
5. Santoro N. Efficacy and safety of intravenous pulsatile gonadotropin-releasing hormone: Lutrepulse for injection. *Am J Obstet Gynecol* 1990; **163:** 1759–64.
6. Nachtigall LB, *et al.* Adult-onset idiopathic hypogonadotropic hypogonadism–a treatable form of male infertility. *N Engl J Med* 1997; **336:** 410–15.

Malignant neoplasms. Gonadorelin analogues are used in the treatment of prostatic cancer (p.671) where they provide an alternative to orchidectomy in the management of advanced disease. They may also be used for ovarian ablation in premenopausal women with breast cancer (p.661). Gonadorelin analogues have been tried in neoplasms of the endometrium (p.663) and ovary, but their use is much less well established.

Analogues used include buserelin (p.2084), goserelin (p.2108), leuprorelin (p.2112), and triptorelin (p.2136).

Mastalgia. Gonadorelin analogues such as goserelin may be effective in severe refractory mastalgia (p.2092).

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.

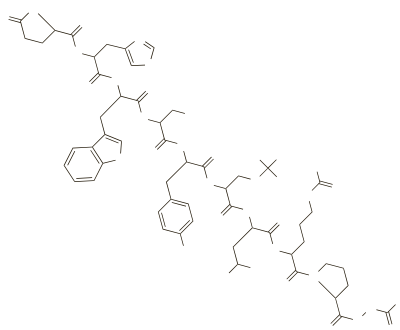
Гозерелин

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