For a general discussion of the management of infertility, see p.2080.

1. Armitage M, *et al.* Successful treatment of infertility due to polycystic ovary disease using a combination of luteinising hormone releasing hormone agonist and low dosage menotrophin. *BMJ* 1987; **295:** 96.
2. Owen EJ, *et al.* The use of a short regimen of buserelin, a gonadotrophin-releasing hormone agonist, and human menopausal gonadotrophin in assisted conception cycles. *Hum Reprod* 1989; **4:** 749–53.
3. Rutherford AJ, *et al.* Improvement of in vitro fertilisation after treatment with buserelin, an agonist of luteinising hormone releasing hormone. *BMJ* 1988; **296:** 1765–8.
4. Tan S-L, *et al.* Cumulative conception and live-birth rates after in vitro fertilization with and without the use of long, short, and ultrashort regimens of the gonadotrophin-releasing hormone agonist buserelin. *Am J Obstet Gynecol* 1994; **171:** 513–20.
5. Urbancsek J, Witthaus E. Midluteal buserelin is superior to early follicular phase buserelin in combined gonadotropin-releasing hormone analog and gonadotropin stimulation in in vitro fertilization. *Fertil Steril* 1996; **65:** 966–71.

Malignant neoplasms. The long-term use of buserelin in men decreases the testicular concentration of testosterone. For this reason it is used in the treatment of prostatic cancer (p.671), which is androgen-dependent.[1] Gonadorelin analogues are an effective alternative to orchidectomy, sometimes combined with an anti-androgen for enhanced effect, and play a major role in the management of advanced, incurable disease.

Other reports of malignant neoplasms treated with buserelin include its use in metastatic breast cancer[2,3] (p.661).

1. de Voogt HJ, *et al.* The use of the LHRH-analogue buserelin in the treatment of prostatic cancer: a 10-year review on 1522 patients treated in 119 centers on 4 continents. *Scand J Urol Nephrol Suppl* 1991; **138:** 131–6.
2. Falkson CI, *et al.* Cyclophosphamide, doxorubicin and fluorouracil (CAF) plus depo-buserelin in the treatment of premenopausal women with metastatic breast cancer. *Ann Oncol* 1992; **3:** 849–53.
3. Klijn JG, *et al.* Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. *J Natl Cancer Inst* 2000; **92:** 903–11.

Porphyria. Buserelin given with medroxyprogesterone acetate suppressed cyclic and premenstrual exacerbations of porphyria (p.1448) in 2 patients. Doses used were 300 micrograms buserelin intranasally in the evenings of days 1 to 21 of the menstrual cycle and 10 mg medroxyprogesterone acetate daily by mouth from day 12 to 21. Both patients were free from porphyric attacks during the reported 11 months of treatment.[1] Intranasal buserelin has also been used in 1 patient to prevent premenstrual exacerbation of coproporphyria.[2] The initial dose of 900 micrograms daily could be tapered to 150 micrograms daily, with only 1 minor attack in 5 years of treatment. The authors of this report also noted a number of case reports of buserelin used in acute intermittent porphyria.

1. Bargetzi MJ, *et al.* Premenstrual exacerbations in hepatic porphyria: prevention by intermittent administration of an LH-RH agonist in combination with a gestagen. *JAMA* 1989; **261:** 864.
2. Yamamori I, *et al.* Prevention of premenstrual exacerbation of hereditary coproporphyria by gonadotropin-releasing hormone analogue. *Intern Med* 1999; **38:** 365–8.

Precocious puberty. The gonadorelin analogues have largely replaced other treatments in the management of central precocious puberty (p.2081). References to the use of buserelin.

1. Drop SLS, *et al.* The effect of treatment with an LH-RH agonist (buserelin) on gonadal activity growth and bone maturation in children with central precocious puberty. *Eur J Pediatr* 1987; **146:** 272–8.
2. Cacciari E, *et al.* Long-term follow-up and final height in girls with central precocious puberty treated with luteinizing hormone-releasing hormone analogue nasal spray. *Arch Pediatr Adolesc Med* 1994; **148:** 1194–9.
3. Juul A, *et al.* Serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 levels are increased in central precocious puberty: effects of two different treatment regimens with gonadotropin-releasing hormone agonists, without or in combination with an antiandrogen (cyproterone acetate). *J Clin Endocrinol Metab* 1995; **80:** 3059–67.
4. Bertelloni S, *et al.* Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr* 1998; **157:** 363–7.
5. Tuvemo T, *et al.* Suppression of puberty in girls with short-acting intranasal versus subcutaneous depot GnRH agonist. *Horm Res* 2002; **57:** 27–31.

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

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Suprefact; ***Austria:*** Suprecur; Suprefact; ***Belg.:*** Suprefact; ***Braz.:*** Suprefact; ***Canad.:*** Suprefact; ***Cz.:*** Suprecur†; Suprefact†; ***Denm.:*** Suprecur; Suprefact; ***Fin.:*** Suprecur; Suprefact; ***Fr.:*** Bigonist; Suprefact; ***Ger.:*** Profact; Suprecur; ***Gr.:*** Suprefact; ***Hong Kong:*** Suprecur; ***Hung.:*** Suprefact; ***Irl.:*** Suprecur; Suprefact; ***Israel:*** Suprefact; ***Ital.:*** Suprefact; ***Jpn:*** Suprecur; ***Malaysia:*** Suprefact; ***Mex.:*** Suprefact; ***Neth.:*** Suprecur†; Suprefact; ***Norw.:*** Suprecur; Suprefact; ***NZ:*** Suprefact; ***Port.:*** Suprefact; ***S.Afr.:*** Suprefact; ***Singapore:*** Suprefact; ***Spain:*** Suprefact; ***Swed.:*** Suprecur; Suprefact; ***Switz.:*** Suprefact; ***Thai.:*** Suprefact; ***Turk.:*** Suprecur; Suprefact; ***UK:*** Suprecur; Suprefact.

Cetrorelix Acetate *(BANM, USAN, rINNM)*

Acetato de cetrorelix; Cétrorélix, Acétate de; Cetrorelixi Acetas; D-20761; NS-75A; SB-75 (cetrorelix); SB-075 (cetrorelix). *N*-Acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^5-carbamoyl-D-ornithyl-L-leucyl-L-arginyl-L-prolyl-D-alaninamide acetate.

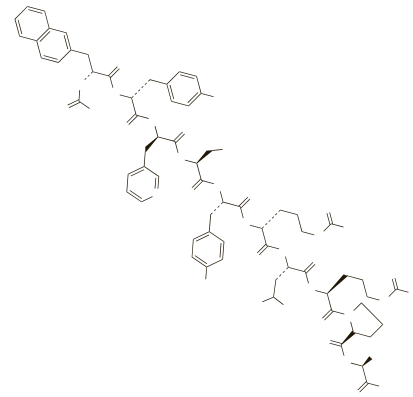
Цетрореликса Ацетат

$C_{70}H_{92}ClN_{17}O_{14}.xC_2H_4O_2$ = 1431.0 (cetrorelix).

CAS — 120287-85-6 (cetrorelix); 145672-81-7 (cetrorelix acetate).

ATC — H01CC02.

ATC Vet — QH01CC02.



(cetrorelix)

Adverse Effects and Precautions

Transient reactions at the injection site, including erythema, pruritus, and swelling, may occur. Nausea and headache have been reported occasionally. Systemic hypersensitivity reactions have been reported rarely.

Cetrorelix should not be used in patients with moderate to severe renal or hepatic impairment.

Pharmacokinetics

The bioavailability of cetrorelix after subcutaneous injection is about 85%. The mean terminal half-life after a subcutaneous injection of 3 mg is about 60 hours; it is less with lower doses (about 5 and 20 hours respectively after single and multiple doses of 250 micrograms).

◊ References.

1. Pechstein B, *et al.* Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers. *J Clin Pharmacol* 2000; **40:** 266–74.
2. Nagaraja NV, *et al.* Pharmacokinetic and pharmacodynamic modeling of cetrorelix, an LH-RH antagonist, after subcutaneous administration in healthy premenopausal women. *Clin Pharmacol Ther* 2000; **68:** 617–25.

Uses and Administration

Cetrorelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist used as a component of ovarian stimulation regimens for assisted reproduction in infertility (p.2080); it is used to prevent luteinising hormone surges and premature ovulation. It has also been tried in benign prostatic hyperplasia, malignant neoplasms of the prostate, endometriosis, and for uterine fibroids. Cetrorelix is given by subcutaneous injection as the acetate; an intramuscular depot formulation containing cetrorelix embonate is reported to be under development. For assisted reproduction, doses of cetrorelix acetate equivalent to cetrorelix 250 micrograms daily may be given either in the morning beginning on day 5 or 6 of ovarian stimulation or in the evening beginning on day 5, and continued until ovulation induction. Alternatively a single dose equivalent to 3 mg of cetrorelix may be given on day 7; if follicle growth does not allow ovulation induction within 4 days, additional doses of cetrorelix 250 micrograms once daily may be given until the day of ovulation induction.

◊ References.

1. Gonzalez-Barcena D, *et al.* Treatment of uterine leiomyomas with luteinizing hormone-releasing hormone antagonist cetrorelix. *Hum Reprod* 1997; **12:** 2028–35.
2. Comaru-Schally AM, *et al.* Efficacy and safety of luteinizing hormone-releasing hormone antagonist cetrorelix in the treatment of symptomatic benign prostatic hyperplasia. *J Clin Endocrinol Metab* 1998; **83:** 3826–31.
3. Felberbaum RE, *et al.* Treatment of uterine fibroids with a slow-release formulation of the gonadotrophin releasing hormone antagonist cetrorelix. *Hum Reprod* 1998; **13:** 1660–8.
4. Huirne JAF, Lambalk CB. Gonadotropin-releasing-hormone-receptor antagonists. *Lancet* 2001; **358:** 1793–1803.
5. Ludwig M, *et al.* Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol: meta-analysis. *Arch Gynecol Obstet* 2001; **265:** 175–82.
6. Roulier R, *et al.* Depot GnRH agonist versus the single dose GnRH antagonist regimen (cetrorelix, 3 mg) in patients undergoing assisted reproduction treatment. *Reprod Biomed Online* 2003; **7:** 185–9.
7. Griesinger G, *et al.* Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; **64:** 563–75.
8. Al-Inany HG, *et al.* Gonadotrophin-releasing hormone antagonists for assisted conception. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 28/07/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cetrotide; ***Austral.:*** Cetrotide; ***Austria:*** Cetrotide; ***Belg.:*** Cetrotide; ***Braz.:*** Cetrotide; ***Canad.:*** Cetrotide; ***Chile:*** Cetrotide; ***Cz.:*** Cetrotide; ***Denm.:*** Cetrotide; ***Fin.:*** Cetrotide; ***Fr.:*** Cetrotide; ***Ger.:*** Cetrotide; ***Gr.:*** Cetrotide; ***Hong Kong:*** Cetrotide; ***Hung.:*** Cetrotide; ***India:*** Cetrotide; ***Indon.:*** Cetrotide; ***Irl.:*** Cetrotide; ***Israel:*** Cetrotide; ***Ital.:*** Cetrotide; ***Malaysia:*** Cetrotide; ***Mex.:*** Cetrotide; ***Neth.:*** Cetrotide; ***Norw.:*** Cetrotide; ***NZ:*** Cetrotide; ***Philipp.:*** Cetrotide; ***Pol.:*** Cetrotide; ***Port.:*** Cetrotide; ***Rus.:*** Cetrotide (Цетротид); ***Singapore:*** Cetrotide; ***Spain:*** Cetrotide; ***Swed.:*** Cetrotide; ***Switz.:*** Cetrotide; ***Thai.:*** Cetrotide; ***Turk.:*** Cetrotide; ***UK:*** Cetrotide; ***USA:*** Cetrotide; ***Venez.:*** Cetrotide.

Chlormadinone Acetate *(BANM, USAN, rINNM)*

Acetato de clormadinona; Chlormadinone, Acétate de; Chlormadinoni Acetas; NSC-92338. 6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate.

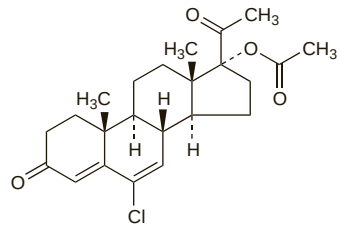
Хлормадинона Ацетат

$C_{23}H_{29}ClO_4$ = 404.9.

CAS — 1961-77-9 (chlormadinone); 302-22-7 (chlormadinone acetate).

ATC — G03DB06.

ATC Vet — QG03DB06.



Pharmacopoeias. In *Chin.*, *Fr.*, and *Jpn.*

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059.

Effects on the skin. A report of auto-immune dermatitis in a patient associated with chlormadinone acetate.[1]

1. Katayama I, Nishioka K. Autoimmune progesterone dermatitis with persistent amenorrhoea. *Br J Dermatol* 1985; **112:** 487–91.

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

Uses and Administration

Chlormadinone acetate is a progestogen structurally related to progesterone (p.2126) that has anti-androgenic activity. It is given either alone or with an oestrogen in the treatment of menstrual disorders such as menorrhagia (p.2126) and endometriosis (p.2091) in oral doses of 2 to 10 mg daily either cyclically or continuously. It may also be used as the progestogen component of combined oral contraceptives (see p.2069) at a dose of 1 to 2 mg daily, particularly in women with androgen-dependent conditions such as acne and hirsutism. Chlormadinone acetate has been used in some countries in the management of prostatic hyperplasia and prostate cancer; oral doses of 25 or 50 mg, respectively have been given twice daily.

◊ Reviews.

1. Curran MP, Wagstaff AJ. Ethinylestradiol/chlormadinone acetate. *Drugs* 2004; **64:** 751–60.
2. Bouchard P. Chlormadinone acetate (CMA) in oral contraception—a new opportunity. *Eur J Contracept Reprod Health Care* 2005; **10** (suppl 1): 7–11.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Luteran; ***Ger.:*** Gestafortin†; ***Jpn:*** Prostal; ***Mex.:*** Lutoral.

Multi-ingredient: ***Chile:*** Belara; Lovinda; ***Cz.:*** Belara; ***Fr.:*** Belara; ***Ger.:*** Balanca; Belara; Esticia; Gestamestrol N†; Neo-Eunomin; Ovosiston†; ***Hung.:*** Belara; ***Israel:*** Belara; ***Ital.:*** Belara; ***Mex.:*** Belara; Lutoral-E; Secuentex-21; ***Port.:*** Belara; Libeli; ***Rus.:*** Belara (Белара); ***Spain:*** Belara; ***Switz.:*** Belara; ***Venez.:*** Belara.