There has been a report of impotence and severe oligospermia associated with ingestion of androstenedione by a bodybuilder.5 Priapism has also been reported.6

- 1. King DS, et al. Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. *JAMA* 1999; **281**: 2020–8.
- 2. Leder BZ, et al. Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 2000; **283**: 779–82.
- 3. Broeder CE, et al. The Andro Project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. Arch Intern Med 2000; 160: 3093-3104.
- 4. Beckham SG, Earnest CP. Four weeks of androstenedione supplementation diminishes the treatment response in middle aged men. Br J Sports Med 2003; 37: 212-8.
- 5. Ritter RH, et al. Oral androstenedione-induced impotence and severe oligospermia. Fertil Steril 2005; 84: 217.e7-e8.
- 6. Kachhi PN, Henderson SO. Priapism after androstenedione intake for athletic performance enhancement. *Ann Emerg Med* 2000; **35:** 391–3.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Thai.: Metharmon-F.

Bazedoxifene Acetate (USAN, rINNM) ⊗

Acetato de bazedoxifeno: Bazédoxifène, Acétate de: Bazedoxifeni Acetas; TSE-424; WAY-140424; WAY-TSE-424. I-{p-[2-(Hexahydro-IH-azepin-I-yl)ethoxy]benzyl}-2-(p-hydroxyphenyl)-3methylindol-5-ol monoacetate.

Базедоксифена Ацетат

(bazedoxifene acetate).

 $C_{30}H_{34}N_2O_3$, $C_2H_4O_2 = 530.7$. 198481-32-2 (bazedoxifene); 198481-33-3

(bazedoxifene)

Profile

Bazedoxifene acetate is a selective oestrogen receptor modulator. It is under investigation in the prevention and treatment of postmenopausal osteoporosis, and with conjugated oestrogens in the management of menopausal vasomotor symptoms, atrophic vaginitis, and postmenopausal osteoporosis.

- Stump AL, et al. Bazedoxifene: a third-generation selective estrogen receptor modulator for treatment of postmenopausal osteoporosis. Ann Pharmacother 2007; 41: 833-9.
- Lewiecki EM. Bazedoxifene and bazedoxifene combined with conjugated estrogens for the management of postmenopausal osteoporosis. Expert Opin Invest Drugs 2007; 16: 1663-72.

Boldenone Undecenoate (BANM, rINNM) ⊗

Ba-29038; Boldenone Undecylenate (USAN); Boldénone, Undécylénate de; Boldenoni Undecylenas; I-Dehydrotestosterone (boldenone); Undecilenato de boldenona. 17β-Hydroxyandrosta-1,4-dien-3-one 17-(undec-10-enoate).

Болденона Ундециленат

 $C_{30}H_{44}O_3 = 452.7.$

CAS — 846-48-0 (boldenone); 13103-34-9 (boldenone undecenoate).

Boldenone undecenoate is an anabolic steroid (see Testosterone. p.2129) that has been used in veterinary practice. It has been subiect to abuse in sport.

Buserelin (BAN, rINN) ⊗

Busereliini; Buserelina; Buserelinas; Buséréline; Buserelinum; Buszerelin; S74-6766. (6-O-tert-Butyl-D-serine)-des-10-glycinamidegonadorelin ethylamide; 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-Lseryl-L-tyrosyl-O-tert-butyl-D-seryl-L-leucyl-L-arginyl-N-ethyl-L-

Бусерелин

 $C_{60}H_{86}N_{16}O_{13} = 1239.4.$

CAS — 57982-77-1.

ATC - LO2AEOI.

ATC Vet - QH01CA90; QL02AE01.

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

Ph. Eur. 6.2 (Buserelin). A white or slightly yellowish hygroscopic powder. Sparingly soluble in water and in dilute acids. Store at 2° to 8°. Protect from light and moisture.

Buserelin Acetate (BANM, USAN, rINNM) ⊗

Acetato de buserelina: Buserelin Asetat: Buséréline, Acétate de: Buserelini Acetas; Hoe-766; D-Ser (Bu^t)⁶ Pro⁹ NEt LHRH acetate.

Бусерелина Ацетат

 $C_{60}H_{86}N_{16}O_{13}, C_2H_4O_2 = 1299.5.$

CAS — 68630-75-1. ATC — L02AE01.

ATC Vet - QL02AE01.

Adverse Effects and Precautions As for Gonadorelin, p.2106.

Interactions As for Gonadorelin, p.2107.

Pharmacokinetics

Buserelin is completely absorbed after subcutaneous injection, with peak plasma concentrations occurring about 1 hour after a dose. It accumulates in liver and kidneys as well as in the anterior pituitary. It is metabolised by tissue peptidases and is excreted in urine and bile as unchanged drug and metabolites. The half-life after injection is stated to be about 80 minutes.

Uses and Administration

Buserelin is an analogue of gonadorelin (p.2107) with similar properties. It is used for the suppression of testosterone in the treatment of malignant neoplasms of the prostate; it is also used in the treatment of endometriosis and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility. It has been used in precocious puberty and tried in the treatment of uterine fibroids (see below). Buserelin is usually given as the acetate but doses are expressed in terms of the base; 105 micrograms of buserelin acetate is equivalent to about 100 micrograms of buserelin.

In advanced prostatic carcinoma doses of 500 micrograms are injected subcutaneously every 8 hours for 7 days. On the eighth day treatment is changed to the nasal route; 100 micrograms is sprayed into each nostril 6 times daily (usually before and after meals). An acceptable response should be achieved within 4 to 6 weeks. Since there is an initial increase in circulating testosterone, an anti-androgen such as cyproterone acetate may be given for at least 3 days before beginning buserelin therapy, and continued for at least 3 weeks, to avoid the risk of a disease flare. Longacting subcutaneous depot preparations that release buserelin over a 2- or 3-month period are also availa-

In **endometriosis** a dose of 150 micrograms is sprayed into each nostril three times daily. The usual duration of therapy is 6 months, which should not be exceeded.

In **infertility**, pituitary desensitisation before ovulation induction with gonadotrophins is achieved by giving 150 micrograms intranasally four times daily, beginning either in the early follicular phase (day 1) or midluteal phase (day 21) of the menstrual cycle. Alternatively, 200 to 500 micrograms may be given daily as a subcutaneous injection. Therapy should be continued until pituitary downregulation occurs, which normally takes 1 to 3 weeks; if necessary 300 micrograms four times daily intranasally, or 500 micrograms twice daily subcutaneously may be given. Gonadotrophin treatment is then added to buserelin therapy until an appropriate stage of follicular development, when both are withdrawn and chorionic gonadotrophin is given to induce ovulation.

◊ General reviews.

1. Brogden RN, et al. Buserelin: a review of its pharmacodynamic pharmacokinetic properties, and clinical profile. Drugs

Endometriosis. Gonadorelin analogues such as buserelin have a role in the management of endometriosis (p.2091), but the need for long-term therapy limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References.

- 1. Lemay A, et al. Efficacy of intranasal or subcutaneous luteinizing hormone-releasing hormone agonist inhibition of ovarian function in the treatment of endometriosis. Am J Obstet Gynecol
- Donnez J, et al. Administration of nasal buserelin as compared with subcutaneous buserelin implant for endometriosis. Fertil Steril 1989; 52: 27–30.
- 3. Nieto A, et al. Long term follow-up of endometriosis after two different therapies (gestrinone and buserelin). Clin Exp Obstet Gynecol 1996; 23: 198–204.
- Regidor P-A, et al. Long-term follow-up on the treatment of endometriosis with the GnRH-agonist buserelin acetate. Eur J Obstet Gynecol Reprod Biol 1997; 73: 153–60.
- Takeuchi H, et al. A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH ago-nists in cases of uterine leiomyomas or endometriosis. J Obstet Gynaecol Res 2000; 26: 325-31.

Fibroids. Like other gonadorelin analogues (see also p.2107) buserelin has been used to reduce the volume of uterine fibroids.

- 1. Maheux R, et al. Use of intranasal luteinizing hormone-releasing hormone agonist in uterine leiomyomas. Fertil Steril 1987; 47:
- Matta WHM, et al. Long-term follow-up of patients with uterine fibroids after treatment with the LHRH agonist buserelin. Br J Obstet Gynaecol 1989; 96: 200-6.
- 3. Fedele L, et al. Intranasal buserelin versus surgery in the treatment of uterine leiomyomata: long-term follow-up. Eur J Obstet Gynecol Reprod Biol 1991; 38: 53–7.
- 4. Ueki M, et al. Endocrinological and histological changes after treatment of uterine leiomyomas with danazol or buserelin. J Obstet Gynaecol 1995; **21:** 1–7.

Infertility. Buserelin is given with gonadotrophic hormone therapy for induction of ovulation and as an aid to improving IVF procedures. Buserelin with gonadotrophic hormones has been found to result in pregnancies in women previously unresponsive to clomifene citrate, 1,2 although there may be a greater risk of multiple births.3

The regimens used in IVF may be characterised according to how long the gonadorelin analogue is given for:

- · long, 2 weeks or more
- · short, 8 to 10 days
- · ultrashort, 3 days

A comparative study of such regimens found that the best results in all age groups were consistently associated with the long buserelin protocol. The timing of buserelin dosage may also be important. Starting buserelin in the midluteal phase of the cycle has been reported to produce more rapid pituitary down regulation and higher pregnancy rates from IVF than when buserelin was begun in the early follicular phase.5

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
- 2. Owen EJ, et al. The use of a short regimen of buserelin, a gona-dotrophin-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 ag-onist 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 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. 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 premen sal women with metastatic breast cancer. Ann Oncol 1992; 3: 849_53
- Klijn JG, et al. Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a rand-omized 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. 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 în 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 pu-berty: 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.
- Bertelloni S, et al. Effect of central precocious puberty and go-nadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. Eur J Pediatr 1998; 157:
- 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.

Proprietary Preparations (details are given in Part 3)

Arg.: Suprefact; Austria: Suprecur; Suprefact; Belg.: Suprefact; Braz.: Suprefact; Austria: Suprecur; Suprefact; Enz.: Suprefact; Fin.: Suprecur; Suprefact; Fin.: Suprecur; Suprefact; Fin.: Suprecur; Suprefact; Fin.: Suprecur; Suprefact; Ind.: Suprefact

Switz.: Suprefact; Thai.: Suprefact; Turk.: Suprecur; Suprefact; UK: Suprecur; Suprefact.

Cetrorelix Acetate (BANM, USAN, rINNM)

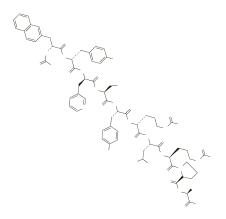
Acetato de cetrorelix; Cétrorélix, Acétate de; Cetrorelixi Acetas; D-20761; NS-75A; SB-75 (cetrorelix); SB-075 (cetrorelix). N-Acetyl-3-(2-naphthyl)-D-alanyl-p-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N5-carbamoyl-D-ornithyl-L-leucyl-L-arginyl-L-prolyl-D-alaninamide acetate.

Цетрореликса Ацетат

 $C_{70}H_{92}CIN_{17}O_{14}$, $xC_2H_4O_2 = 1431.0$ (cetrorelix). CAS — 120287-85-6 (cetrorelix); 145672-81-7 (cetrorelix acetate).

ATC — HÓICCO2

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).

- 1. Pechstein B, et al. Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers. J Clin Pharmacol 2000; 40:
- 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.

- Gonzalez-Barcena D, et al. Treatment of uterine leiomyomas with luteinizing hormone-releasing hormone antagonist cetrore-lix. 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 Endo-crinol Metab 1998; 83: 3826–31.
- 3. Felberbaum RE, et al. Treatment of uterine fibroids with a slowrelease formulation of the gonadotrophin releasing hormone antagonist cetrorelix. *Hum Reprod* 1998; **13:** 1660–8.

- Huirne JAF, Lambalk CB. Gonadotropin-releasing-hormone-re-ceptor antagonists. *Lancet* 2001; 358: 1793–1803.
- 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.
- 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.
- Griesinger G, et al. Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differenc-es between agents? Drugs 2004; 64: 563–75.
- 8. Al-Inany HG, et al. Gonadotrophin-releasing hormone antagonists for assisted conception. Available in The Cochrane Data-base of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 28/07/08).

Preparations

Proprietary Preparations (details are given in Part 3)

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;
Cetrotide; Hong Kong: Cetrotide; Hung.: Cetrotide; India: Cetrotide;
Indon.: Cetrotide; Irl.: Cetrotide; Strael: Cetrotide; India: Cetrotide;
NZ: Cetrotide; Mex.: Cetrotide; Neth.: Cetrotide; Now.: Cetrotide;
NZ: Cetrotide; Philipp.: Cetrotide; Port.: Cetrotide;
Rus.: Cetrotide; Switz.: Cetrotide;
Nach: Cetrotide; Turk.: Cetrotide;
Nach: Cetrotide; Usa: Cetrotide;
Nach: Cetrotide; Visa: Cetrotide; Visa: Cetrotide;
Nach: Cetrotide; Visa: Cetrotide; Visa: Cetrotide;
Nach: Cetrotide; Visa: 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

 $C_{23}H_{29}CIO_4 = 404.9.$

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

rmadinone 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.

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

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; Portz. Belara; Libeli; Rus.: Belara (Белара); Spain: Belara; Switz.: Belara; Venez.: Belara.