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.

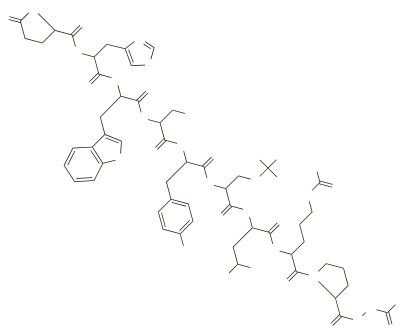
Гозерелин

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

2. Akaza H. Adjuvant goserelin improves clinical disease-free survival and reduces disease-related mortality in patients with locally advanced or localized prostate cancer. *BJU Int* 2004; **93:** 42–6.
3. Taylor CW, *et al.* Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998; **16:** 994–9.
4. Klijn JGM, *et al.* Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; **19:** 343–53.
5. Jakesz R, *et al.* Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002; **20:** 4621–7.
6. Jonat W, *et al.* Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. *J Clin Oncol* 2002; **20:** 4628–35.
7. International Breast Cancer Study Group (IBCSG). Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003; **95:** 1833–46.
8. Cheer SM, *et al.* Goserelin: a review of its use in the treatment of early breast cancer in premenopausal and perimenopausal women. *Drugs* 2005; **65:** 2639–55.
9. Baum M, *et al.* ZIPP International Collaborators' Group. Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. *Eur J Cancer* 2006; **42:** 895–904.

Mastalgia. For reference to the use of goserelin in mastalgia, see under Danazol, p.2092.

Premenstrual syndrome. For reference to the use of goserelin 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.: Larmadex; Zoladex; ***Austral.:*** Zoladex; ***Austria:*** Zoladex; ***Belg.:*** Zoladex; ***Braz.:*** Zoladex; ***Canad.:*** Zoladex; ***Chile:*** Vacromil; Zoladex; ***Cz.:*** Zoladex; ***Denm.:*** Zoladex; ***Fin.:*** Zoladex; ***Fr.:*** Zoladex; ***Ger.:*** Zoladex; ***Gr.:*** Zoladex; ***Hong Kong:*** Zoladex; ***Hung.:*** Zoladex; ***Indon.:*** Zoladex; ***Irl.:*** Zoladex; ***Israel:*** Zoladex; ***Ital.:*** Zoladex; ***Malaysia:*** Zoladex; ***Mex.:*** Zoladex; ***Neth.:*** Zoladex; ***Norw.:*** Zoladex; ***NZ:*** Zoladex; ***Philipp.:*** Zoladex; ***Pol.:*** Zoladex; ***Port.:*** Zoladex; ***Rus.:*** Zoladex (Золадекс); ***S.Afr.:*** Zoladex; ***Singapore:*** Zoladex; ***Spain:*** Zoladex; ***Swed.:*** Zoladex; ***Switz.:*** Zoladex; ***Thai.:*** Zoladex; ***Turk.:*** Zoladex; ***UK:*** Zoladex; ***USA:*** Zoladex; ***Venez.:*** Zoladex.

Multi-ingredient: ***Austral.:*** Zolacos CP.

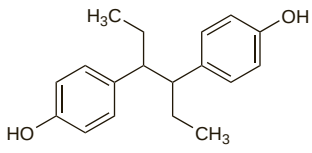
Hexestrol *(rINN)*

Dihydrodiethylstilboestrol; Dihydrostilboestrol; Hexanoestrol; Hexestrolum; Hexoestrol; NSC-9894; Synestrol; Synoestrol. 4,4′-(1,2-Diethylethylene)diphenol.

Гексэстрол

$C_{18}H_{22}O_2$ = 270.4.

CAS — 5635-50-7 (hexestrol); 84-16-2 (meso-hexestrol).



Profile

Hexestrol is a synthetic nonsteroidal oestrogen that is used in the treatment of malignant neoplasms and gynaecological disorders.

Histrelin *(USAN, rINN)* ⊗

Histrelina; Histréline; Histrelinum; ORF-17070; RWJ-17070. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*N* -benzyl-D-histidyl-L-leucyl-L-argininyl-*N*-ethyl-L-prolinamide.

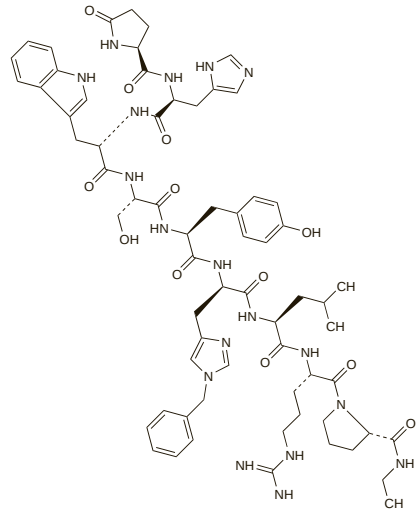
Гистрелин

$C_{66}H_{86}N_{18}O_{12}$ = 1323.5.

CAS — 76712-82-8.

ATC — H01CA03.

ATC Vet — QH01CA03.



Histrelin Acetate *(rINNM)* ⊗

Acetato de histrelina; Histréline, Acétate d'; Histrelini Acetas.

Гистрелина Ацетат

$C_{66}H_{86}N_{18}O_{12}.xC_2H_4O_2.yH_2O$.

CAS — 220810-26-4.

ATC — H01CA03.

ATC Vet — QH01CA03.

Adverse Effects and Precautions

As for Gonadorelin, p.2106.

Uses and Administration

Histrelin is an analogue of gonadorelin (p.2107) with similar properties. A subcutaneous implant containing histrelin acetate 50 mg, and designed to release histrelin acetate 50 to 60 micrograms daily for 12 months, is used in the palliative treatment of advanced prostate cancer (p.671).

Histrelin is used in the treatment of precocious puberty in children (see below). It has also been investigated in disorders related to the menstrual cycle, and in the treatment of acute porphyrias.

◊ References.

1. Anderson KE, *et al.* A gonadotropin releasing hormone analogue prevents cyclical attacks of porphyria. *Arch Intern Med* 1990; **150:** 1469–74.
2. Mortola JF, *et al.* Successful treatment of severe premenstrual syndrome by combined use of gonadotropin-releasing hormone agonist and estrogen/progestin. *J Clin Endocrinol Metab* 1991; **72:** 252A–F.
3. Cheung AP, Chang RJ. Pituitary responsiveness to gonadotrophin-releasing hormone agonist stimulation: a dose-response comparison of luteinizing hormone/follicle-stimulating hormone secretion in women with polycystic ovary syndrome and normal women. *Hum Reprod* 1995; **10:** 1054–9.
4. Chertin B, *et al.* An implant releasing the gonadotropin hormone-releasing hormone agonist histrelin maintains medical castration for up to 30 months in metastatic prostate cancer. *J Urol (Baltimore)* 2000; **163:** 838–44.
5. Schlegel PN, *et al.* Effective long-term androgen suppression in men with prostate cancer using a hydrogel implant with the GnRH agonist histrelin. *Urology* 2001; **58:** 578–82.
6. Dineen MK, *et al.* An evaluation of the pharmacokinetics and pharmacodynamics of the histrelin implant for the palliative treatment of prostate cancer. *J Clin Pharmacol* 2005; **45:** 1245–9.
7. Schlegel PN. Histrelin Study Group. Efficacy and safety of histrelin subdermal implant in patients with advanced prostate cancer. *J Urol (Baltimore)* 2006; **175:** 1353–8.

Administration in children. For the suppression of gonadal sex hormone production in children with central precocious puberty (p.2081), histrelin acetate has been given by subcutaneous injection in usual doses equivalent to histrelin 10 micrograms/kg daily. Alternatively, a subcutaneous implant containing histrelin acetate 50 mg and designed to release histrelin acetate 65 micrograms daily for 12 months may be used. The implant is not recommended for children under 2 years of age.

References.

1. Barradell LB, McTavish D. Histrelin: a review of its pharmacological properties and therapeutic role in central precocious puberty. *Drugs* 1993; **45:** 570–88.
2. Feuillan PP, *et al.* Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *J Clin Endocrinol Metab* 1999; **84:** 44–9.
3. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; **86:** 4711–16.
4. Hirsch HJ, *et al.* The histrelin implant: a novel treatment for central precocious puberty. Abstract: *Pediatrics* 2005; **116:** 1534–5. Full version: http://pediatrics.aappublications.org/cgi/reprint/116/6/e798 (accessed 04/12/07)
5. Eugster EA, *et al.* Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. *J Clin Endocrinol Metab* 2007; **92:** 1697–1704.

Preparations

Proprietary Preparations (details are given in Part 3)

Malaysia: Vantas; ***USA:*** Supprelin; Vantas.

Human Menopausal Gonadotrophins *(BAN)* ⊗

Gonadotropina menopáusica humana; HMG; Org-31338; Urogonadotrophin.

ATC — G03GA02.

ATC Vet — QG03GA02.

Description. A purified extract of human postmenopausal urine containing follicle-stimulating hormone (FSH) and luteinising hormone (LH); the relative *in-vivo* activity is expressed as a ratio. Human menopausal gonadotrophins with a ratio of FSH:LH of 1:1 are known as menotrophin (see below).

Menotrophin *(BAN)* ⊗

Menotropiini; Menotropin; Menotropina; Menotropins *(USAN)*; Menotropinum.

CAS — 9002-68-0.

Pharmacopoeias. In *Br.*, *Chin.*, *Jpn*, and *US*.

BP 2008 (Menotrophin). A dry preparation containing glycoprotein gonadotrophins possessing follicle-stimulating and luteinising activities. It contains not less than 40 units of follicle-stimulating hormone activity per mg. The ratio of units of luteinising hormone activity to units of follicle-stimulating hormone activity is about 1. The preparation is exclusively or predominantly of pituitary origin and obtained from the urine of postmenopausal women but, when necessary, chorionic gonadotrophin obtained from the urine of pregnant women may be added to achieve the above ratio. An almost white or slightly yellow powder. Soluble in water. Store in airtight containers. Protect from light.

USP 31 (Menotropins). An extract of human postmenopausal urine containing both follicle-stimulating hormone and luteinising hormone. It has a potency of not less than 40 follicle-stimulating hormone units and not less than 40 luteinising hormone units per mg. The ratio of units is about 1. Chorionic Gonadotropin obtained from the urine of pregnant women may be added to achieve this ratio. Not more than 30% of the luteinising hormone activity is contributed by Chorionic Gonadotropin. Store in airtight containers at 2° to 8°.

Adverse Effects

Human menopausal gonadotrophins may cause dose-related ovarian hyperstimulation varying from mild ovarian enlargement and abdominal discomfort to severe hyperstimulation with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock and thromboembolic disorders. Rupture of ovarian cysts and intraperitoneal haemorrhage has occurred, usually after pelvic examination. Fatalities have been reported.

Hypersensitivity reactions and local reactions at the injection site may occur. Nausea and vomiting, joint pains and fever have been reported; gynaecomastia, acne, and weight gain have occurred in men.

Carcinogenicity. In a case-control study of 4575 women with primary invasive breast cancer, an evaluation of risk factors found that, overall, the use of infertility drugs was not associated with an increased risk of breast cancer.[1] However, subgroup analysis of individual drugs found that the use of human menopausal gonadotrophins for at least 6 months or 6 treatment cycles was associated with a risk of breast cancer that was 2 to 3 times greater than for women who had never received any fertility treatment. The authors of this study noted that these results were based on small numbers and that other studies had failed to show an association between fertility treatment and breast cancer.

1. Burkman RT, *et al.* Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. *Fertil Steril* 2003; **79:** 844–51.

Effects on the ovary. Ovarian hyperstimulation syndrome after use of human menopausal gonadotrophins in 4 women progressed to acute adnexal torsion.[1] Deep-vein thrombosis has also been a rare complication of ovarian hyperstimulation syndrome associated with the use of human menopausal gonadotrophins