Fosfestrol Sodium *(BANM, rINNM)*

Fosfestrol sódico; Fosfestrol Sodique; Natrii Fosfestrolum.

Натрий Фосфэстрол

$C_{18}H_{18}Na_4O_8P_2$ = 516.2.

CAS — 23519-26-8 (fosfestrol tetrasodium xH_2O); 4719-75-9 (anhydrous fosfestrol tetrasodium).

ATC — L02AA04.

ATC Vet — QL02AA04.

Pharmacopoeias. In *Br.*, which specifies xH_2O.

BP 2008 (Fosfestrol Sodium). A white or almost white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether. A 5% solution in water has a pH of 7.0 to 9.0. Protect from light.

Adverse Effects and Precautions

As for Diethylstilbestrol, see p.2094.

After intravenous injection of fosfestrol sodium there may be a temporary burning sensation in the perineal region and pain at the site of bony metastases. Slow infusion is not recommended as cytotoxic concentrations of the drug may not be achieved.

Uses and Administration

Fosfestrol is a synthetic nonsteroidal oestrogen that requires dephosphorylation to diethylstilbestrol (p.2094) before it is active. It is used in the treatment of malignant neoplasms of the prostate (p.671).

Fosfestrol and its sodium salt have both been used, and doses of fosfestrol sodium may be expressed in terms of either the base or the salt; anhydrous fosfestrol sodium 300 mg is equivalent to about 250 mg of fosfestrol. Expressed in terms of fosfestrol sodium, initial doses of 600 to 1200 mg daily by slow intravenous injection over about 1 hour may be given for 5 to 10 days, followed by 300 mg daily for 10 to 20 days. Injections should be given preferably with the patient lying down. Maintenance intravenous doses of fosfestrol sodium 300 to 600 mg may be given, reduced gradually over several months from dosing 4 times a week to once weekly. Fosfestrol sodium may also be given orally. If initial doses cannot be given intravenously, doses of 360 to 480 mg three times daily have been given orally. For maintenance therapy, doses of 120 to 240 mg three times daily may be used, and gradually reduced to 240 mg daily.

Preparations

BP 2008: Fosfestrol Injection; Fosfestrol Tablets;
USP 31: Diethylstilbestrol Diphosphate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fosfostilben†; Honvan†; ***Austria:*** Honvan; ***Belg.:*** Honvan†; ***Braz.:*** Ronvan†; ***Canad.:*** Honvol; ***Fr.:*** ST-52†; ***Ger.:*** Honvan†; ***Gr.:*** Honvan; ***Hong Kong:*** Honvan†; ***India:*** Honvan; ***Mex.:*** Honvan†; ***Neth.:*** Honvan†; ***Port.:*** Honvan†; ***Spain:*** Honvan†; ***Switz.:*** Honvan†.

Ganirelix Acetate *(BANM, USAN, rINNM)*

Acetato de ganirelix; Ganirélix, Acétate de; Ganirelixi Acetas; Org-37462; RS-26306. *N*-Acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^6-(*N,N′*-diethylamidino)-D-lysyl-L-leucyl-N^6-(*N,N′*-diethylamidino)-L-lysyl-L-prolyl-D-alaninamide acetate.

Ганиреликса Ацетат

$C_{80}H_{113}ClN_{18}O_{13}$,2$C_2H_4O_2$ = 1690.4.

CAS — 124904-93-4 (ganirelix); 129311-55-3 (ganirelix acetate).

ATC — H01CC01.

ATC Vet — QH01CC01.

Adverse Effects and Precautions

As for Cetrorelix, p.2084.

Pharmacokinetics

Ganirelix is rapidly absorbed after subcutaneous injection, with a bioavailability of about 91%. It is metabolised by enzymatic hydrolysis and about 75% of a dose is excreted as metabolites in the faeces. Unchanged drug is found in the urine. The elimination half-life of ganirelix is about 13 hours.

◊ References.

1. Oberyé JJL, *et al.* Pharmacokinetic and pharmacodynamic characteristics of ganirelix (Antagon/Orgalutron) part I: absolute bioavailability of 0.25 mg of ganirelix after a single subcutaneous injection in healthy female volunteers. *Fertil Steril* 1999; **72:** 1001–5.

Uses and Administration

Like cetrorelix (p.2084), ganirelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is used as a component of ovarian stimulation regimens for assisted reproduction in infertility (p.2080); ganirelix acetate is given by subcutaneous injection to prevent premature luteinising hormone surges. Doses are expressed in terms of the acetate or the equivalent amount of base. Ganirelix acetate 108 mg is equivalent to about 100 mg of ganirelix. In the UK a dose equivalent to ganirelix 250 micrograms is given once daily, starting on day 6 of ovarian stimulation and continued until ovulation induction. In the USA a dose of ganirelix acetate 250 micrograms is used similarly.

◊ References.

1. Gillies PS, *et al.* Ganirelix. *Drugs* 2000; **59:** 107–11.
2. The European Orgalutran Study Group, *et al.* Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. *Hum Reprod* 2000; **15:** 1490–8. Correction. *ibid.*; 1877.
3. The North American Ganirelix Study Group. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. *Fertil Steril* 2001; **75:** 38–45.
4. European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. *Hum Reprod* 2001; **16:** 644–51.
5. Griesinger G, *et al.* Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; **64:** 563–75.
6. Out HJ, *et al.* A randomized, double-blind, multicentre clinical trial comparing starting doses of 150 and 200 IU of recombinant FSH in women treated with the GnRH antagonist ganirelix for assisted reproduction. *Hum Reprod* 2004; **19:** 90–5.
7. Wilcox J, *et al.* CAP IV Investigator Group. Prospective, randomized trial comparing cetrorelix acetate and ganirelix acetate in a programmed, flexible protocol for premature luteinizing hormone surge prevention in assisted reproductive technologies. *Fertil Steril* 2005; **84:** 108–17.
8. Lambalk CB, *et al.* Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial. *Hum Reprod* 2006; **21:** 632–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Orgalutran; ***Austral.:*** Orgalutran; ***Belg.:*** Orgalutran; ***Braz.:*** Orgalutran; ***Canad.:*** Orgalutran; ***Chile:*** Orgalutran; ***Cz.:*** Orgalutran; ***Denm.:*** Orgalutran; ***Fin.:*** Orgalutran; ***Fr.:*** Orgalutran; ***Ger.:*** Orgalutran; ***Gr.:*** Orgalutran; ***Hong Kong:*** Orgalutran; ***Hung.:*** Orgalutran; ***Irl.:*** Orgalutran; ***Israel:*** Orgalutran; ***Ital.:*** Orgalutran; ***Malaysia:*** Orgalutran; ***Mex.:*** Orgalutran; ***Norw.:*** Orgalutran; ***NZ:*** Orgalutran; ***Philipp.:*** Orgalutran; ***Port.:*** Orgalutran; ***Rus.:*** Orgalutran (Оргалутран); ***Singapore:*** Orgalutran; ***Spain:*** Orgalutran; ***Swed.:*** Orgalutran; ***Switz.:*** Orgalutran; ***Thai.:*** Orgalutran; ***Turk.:*** Orgalutran; ***UK:*** Orgalutran; ***USA:*** Antagon†; ***Venez.:*** Orgalutran.

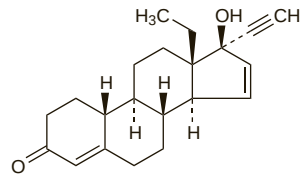
Gestodene *(BAN, USAN, rINN)*

Gestodeeni; Gestoden; Gestodène; Gestodeno; Gestodenum; SH-B-331. 13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one.

Гестоден

$C_{21}H_{26}O_2$ = 310.4.

CAS — 60282-87-3.



Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059. Gestodene is reported to have few androgenic effects, and to have less adverse effect on the serum lipid profile than older 19-nortestosterone derivatives. However, there is some evidence that gestodene-containing combined oral contraceptives are associated with a small increased risk of venous thromboembolism (see p.2063, and for precautions, see under Cardiovascular Disease, p.2066).

Interactions

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

Antiepileptics. *Felbamate* significantly increased gestodene clearance from a low-dose combined oral contraceptive, and might decrease contraceptive efficacy.[1] See also p.2068.

1. Saano V, *et al.* Effects of felbamate on the pharmacokinetics of a low-dose combination oral contraceptive. *Clin Pharmacol Ther* 1995; **58:** 523–31.

Pharmacokinetics

Gestodene is well absorbed with a high bioavailability when given orally. It is extensively bound to plasma proteins; 75 to 87% to sex hormone binding globulin, and 13 to 24% to albumin. Gestodene is metabolised in the liver, less than 1% of a dose being excreted in the urine unchanged. After multiple doses with ethinylestradiol, gestodene has an elimination half-life of about 20 hours.

Uses and Administration

Gestodene is a progestogen (see Progesterone, p.2125) structurally related to levonorgestrel. It is used as the progestogenic component of combined oral contraceptives (see p.2069); a typical daily dose is 75 micrograms in monophasic preparations, and 50 to 100 micrograms in triphasic preparations. Gestodene is also used orally as the progestogenic component of menopausal HRT (see p.2076) in a regimen of 25 or 50 micrograms daily for 12 days of a 28-day cycle.

◊ Reviews.

1. Anonymous. Femodene/Minulet—how different is gestodene? *Drug Ther Bull* 1990; **28:** 41–2.
2. Wilde MI, Balfour JA. Gestodene: a review of its pharmacology, efficacy and tolerability in combined contraceptive preparations. *Drugs* 1995; **50:** 364–95.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Avaden.

Multi-ingredient: ***Arg.:*** Aleli; Biofem; Cuidafem; Femiane; Ginelea; Ginelea T; Gynovin; Harmonet; Livianne; Mesconcept; Minesse; Minulet; Mirelle; Secret 28; Venisse; ***Austral.:*** Femoden ED; Minulet; Tri-Minulet†; Trioden; ***Austria:*** Gynovin; Harmonette; Meliane; Minesse; Minulet; Mirelle; Myvlar; Tri-Minulet; Triodena; Yris; ***Belg.:*** Femodene; Gestodelle; Gestofeme; Harmonet; Meliane; Minulet; Mirelle; Tri-Minulet; Triodene; ***Braz.:*** Adoless; Alexa; Allestra; Diminut; Femiane; Fertnon; Gestinol; Ginesse; Gynera; Harmonet; Micropil; Minesse; Minima; Minulet; Mirelle; Previane; Siblima; Tamisa; ***Chile:*** Avaden; Careza; Ciclomex; Feminol; Gynera; Harmonet; Microgen; Minesse; Minigest; Minulet; Mirelle; Tri-Ciclomex; ***Cz.:*** Avaden†; Convaden†; Femoden; Harmonet; Katya; Lindynette; Logest; Lunafem; Milligest; Milvane†; Minesse; Minulet; Mirelle; Sunya; Tri-Minulet; ***Denm.:*** Gestonette; Gynera; Harmonet; Lindynette; Meloden; Milvane; Minulet; Tri-Minulet†; ***Fin.:*** Femoden; Harmonet; Meliane; Minulet; Mirelle; Tri-Femoden; Tri-Minulet†; ***Fr.:*** Avadene; Harmonet; Meliane; Melodia; Minesse; Minulet; Moneva; Phaeva; Successia†; Tri-Minulet; ***Ger.:*** Femovan; Minulet; ***Gr.:*** Gynera; Harmonette; Meliane; Minulet; Tri-Minulet; Trigynera; ***Hong Kong:*** Gynera; Harmonet; Meliane; Minulet†; ***Hung.:*** Femoden; Harmonet; Lindynette; Meliane; Milligest; Minesse; Minulet; Tri-Minulet†; Triodena; ***Indon.:*** Gynera; ***Irl.:*** Femodene†; Minulet; Tri-Minulet; Triodene†; ***Israel:*** Gynera; Harmonet; Meliane; Minesse; Minulet; ***Ital.:*** Arianna; Fedra; Ginoden; Harmonet; Milvane; Minesse; Minulet; Tri-Minulet; ***Malaysia:*** Gynera; Lindynette; Meliane; Minulet; ***Mex.:*** Avaden; Ginelea; Gynovin; Minesse; Minulet; Secret 28; ***Neth.:*** Avaden†; Femodeen; Harmonet†; Meliane; Minulet; Tri-Minulet†; Triodeen; ***NZ:*** Femodene; Melodene; Minulet; ***Philipp.:*** Gynera; Meliane; Minulet; ***Pol.:*** Femoden; Harmonet; Logest; Milvane; Minulet; Mirelle; Tri-Minulet; ***Port.:*** Avadene; Effiplen; Estinette; Gynera; Harmonet; Microgeste; Minesse; Minigeste; Minulet; Tri-Gynera; Tri-Minulet; ***Rus.:*** Femoden (Фемоден); Lindynette (Линдинет); Logest (Логест); ***S.Afr.:*** Femodene ED; Harmonet; Melodene; Minesse; Minulette; Mirelle; Tri-Minulet; Triodene; ***Singapore:*** Gynera; Meliane; Minulet; ***Spain:*** Gynovin; Harmonet; Meliane; Melodene 15; Minesse; Minulet; Tri-Minulet; Trigynovin; ***Switz.:*** Gynera; Harmonet; Meloden; Milvane; Minesse; Minulet; Mirelle; Tri-Minulet; ***Thai.:*** Gynera; Meliane; Minulet†; ***Turk.:*** Ginera; Minulet; ***UK:*** Femodene; Femodette; Katya; Minulet†; Sunya; Tri-Minulet†; Triadene; ***Venez.:*** Avaden; Femiane; Gynera; Harmonet; Minesse; Minulet; Mirelle.

Gestonorone Caproate *(BANM, USAN, rINN)*

Caproato de gestonorona; Caproato de gestronol; Gestonorone, caproate de; Gestonoroni caproas; Gestronol Hexanoate; Hexanoato de gestonorona; Hexanoato de gestronol; NSC-84054; SH-582. 17α-Hydroxy-19-norpregn-4-ene-3,20-dione hexanoate.

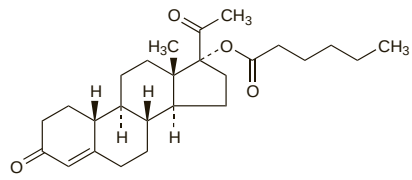
Гестонорона Капроат

$C_{26}H_{38}O_4$ = 414.6.

CAS — 1253-28-7.

ATC — G03DA01; L02AB03.

ATC Vet — QG03DA01; QL02AB03.



Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125).

Local reactions have occurred at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may develop during or immediately after injection but can be avoided by injecting gestonorone very slowly. In males, spermatogenesis is temporarily inhibited.

Interactions

As for progestogens in general (see Progesterone, p.2126).

Uses and Administration

Gestonorone caproate is a long-acting potent progestogen structurally related to progesterone (p.2126). It has been given in an oily solution by intramuscular injection in doses of 200 to 400 mg every 5 to 7 days for the adjunctive treatment of endometrial carcinoma (p.663). It has also been used in the management of benign prostatic hyperplasia (p.2178) in doses of 200 mg weekly, increased to 300 to 400 mg weekly if necessary.

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.

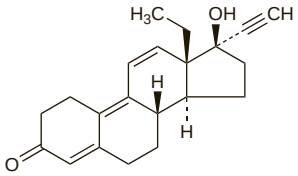
Гестринон

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

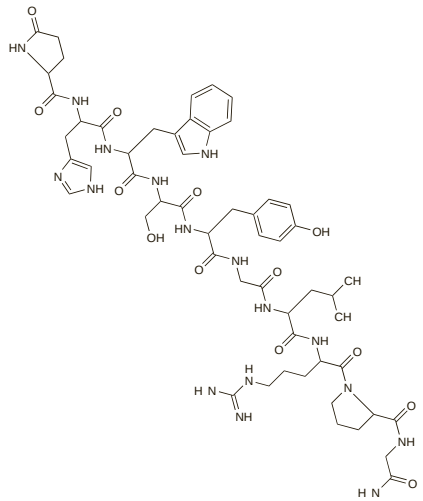
Гонадорелин

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