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.

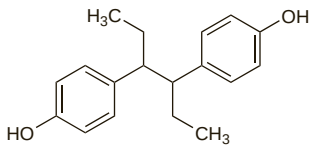
Hexestrol *(rINN)*

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.

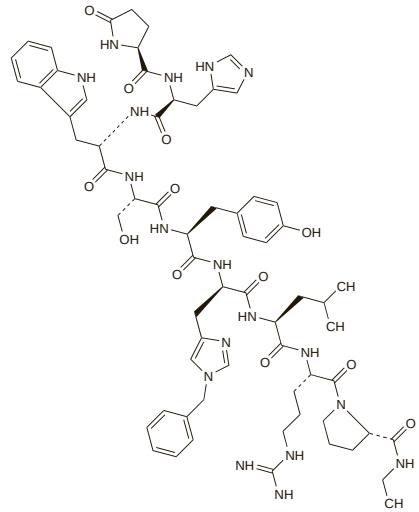
Гистрелин

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

plus chorionic gonadotrophin.[2,3] In another case in which thrombosis followed the use of human menopausal gonadotrophins alone, hereditary activated protein C resistance and smoking may have been contributing factors.[4]

1. Kemmann E, *et al*. Adnexal torsion in menotropin-induced pregnancies. *Obstet Gynecol* 1990; **76:** 403–6.
2. Kaaja R, *et al.* Severe ovarian hyperstimulation syndrome and deep venous thrombosis. *Lancet* 1989; **ii:** 1043.
3. Sobande AA, *et al*. Ovarian hyperstimulation syndrome and deep vein thrombosis. *Saudi Med J* 2000; **21:** 783–4.
4. Ludwig M, *et al*. Deep vein thrombosis during administration of HMG for ovarian stimulation. *Arch Gynecol Obstet* 2000; **263:** 139–41.

Precautions

Human menopausal gonadotrophins should not be given to pregnant patients. Use should be avoided in patients with abnormal genital bleeding, hormone sensitive malignancies such as those of the breast, uterus, prostate, ovaries or testes, or ovarian cysts or enlargement not caused by the polycystic ovary syndrome. Pituitary or hypothalamic lesions, adrenal or thyroid disorders, and hyperprolactinaemia should be treated appropriately to exclude them as causes of infertility before attempting therapy with human menopausal gonadotrophins. Patients who experience ovarian enlargement are at risk of rupture; pelvic examinations should be avoided or carried out with care and the recommendation has been made that sexual intercourse should be avoided while there is such a risk.

There is a risk of multiple births.

Interactions

In women who show evidence of excessive ovarian stimulation while receiving human menopausal gonadotrophins the use of drugs with luteinising-hormone (LH) activity increases the risk of ovarian hyperstimulation syndrome.

Uses and Administration

Human menopausal gonadotrophins possess both follicle-stimulating hormone (FSH) activity (see p.2104) and luteinising hormone (LH) activity (see p.2112).

Human menopausal gonadotrophins are used in the treatment of male and female infertility due to hypogonadism. In anovulatory infertility unresponsive to clomifene, human menopausal gonadotrophins are given to induce follicular maturation and are followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation, a topic discussed further on p.2080.

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles, or both. Human menopausal gonadotrophins may be given daily by intramuscular or subcutaneous injection to provide a dose of 75 to 150 units of FSH and gradually adjusted if necessary until an adequate response is achieved. Treatment is then stopped and followed after 1 or 2 days by single doses of chorionic gonadotrophin 5000 to 10 000 units (see p.2085). In menstruating patients treatment should be started within the first 7 days of the menstrual cycle. In the UK it has been suggested that the treatment course should be abandoned if no response is seen in 3 weeks although in the US the manufacturers recommend that an individual course should not exceed 12 days. This course may be repeated at least twice more if necessary.

An alternative schedule is to give three equal doses by intramuscular or subcutaneous injection, each providing 225 to 375 units of FSH on alternate days followed by chorionic gonadotrophin one week after the first dose.

In IVF and other assisted conception techniques, human menopausal gonadotrophins are used with chorionic gonadotrophin and sometimes also clomifene citrate or a gonadorelin analogue. Stimulation of follicular growth is produced by human menopausal gonadotrophins given by intramuscular or subcutaneous injection, in a dose providing 75 to 300 units of FSH daily, usually beginning on the 2nd or 3rd day of the menstrual cycle. Treatment is continued until an adequate response is obtained and the final injection of human menopausal gonadotrophins is followed 1 to 2 days later with up to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is carried out about 32 to 36 hours later.

In **men with infertility** due to hypogonadotrophic hypogonadism (see Infertility, p.2080), spermatogenesis is stimulated with chorionic gonadotrophin and then human menopausal gonadotrophins are added in a dose of 75 or 150 units of FSH two or three times weekly by intramuscular or subcutaneous injection. Treatment should be continued for at least 3 or 4 months.

Infertility. Systematic reviews have not found evidence of a significant difference in efficacy for human menopausal gonadotrophins compared with urinary-derived gonadotrophins in women with anovulatory infertility[1] (p.2080), or compared with recombinant follicle-stimulating hormone in assisted reproduction cycles.[2] UK guidelines[3] consider that human menopausal gonadotrophins, urinary follicle-stimulating hormone, and recombinant follicle-stimulating hormone are equally effective in achieving pregnancy for women with ovulatory disorders, such as polycystic ovary syndrome, and for IVF treatment.

1. 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 16/09/05).
2. Van Wely M, *et al.* Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
3. National Collaborating Centre for Women's and Children's Health/NICE. Fertility: assessment and treatment for people with fertility problems. February 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 28/07/08)

Preparations

BP 2008: Menotrophin Injection;
USP 31: Menotropins for Injection.

Proprietary Preparations (details are given in Part 3)

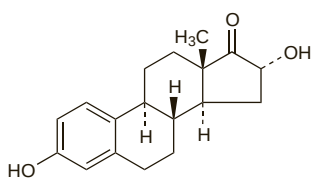
Arg.: HMG Ferring; Lifecell; Menopur; Pergonal†; ***Austral.:*** Humegon; ***Austria:*** Menopur; ***Belg.:*** Menopur; ***Braz.:*** Menogon†; Menopur†; Merional-HMG†; Pergonal; ***Canad.:*** Humegon†; Pergonal†; Repronex; ***Chile:*** Menopur; Pergonal†; ***Cz.:*** Humegon†; Menogon; Menopur; Merional; ***Denm.:*** Menogon†; Menopur; ***Fin.:*** Menogon†; Menopur; ***Fr.:*** Menopur; ***Ger.:*** Humegon†; Menogon; ***Gr.:*** Altermon; Menogon; Menopur; Merional; Pergogreen†; Pergonal†; ***Hong Kong:*** Menogon; Menopur; Merional; Pergonal; ***Hung.:*** Menogon†; Menopur; Merional; ***India:*** Eventin; Pergonal; Pregnorm; ***Irl.:*** Humegon; Menogon†; Menopur; ***Israel:*** Humegon†; Menogon; Menopur; Pergonal†; ***Ital.:*** Humegon†; Menogon; Meropur; ***Jpn:*** Gonadoryl; ***Malaysia:*** Menopur; ***Mex.:*** Humegon†; Merapur HP; Merional; Pergonal†; ***Neth.:*** Humegon; Menogon; Menopur; Pergonal†; ***Norw.:*** Menopur; ***Pol.:*** Menopur; ***Port.:*** Humegon†; ***Rus.:*** Menogon (Меногон); Menopur (Меопур); Pergonal (Пергонал); ***S.Afr.:*** Humegon†; Pergonal†; ***Singapore:*** Menogon; ***Spain:*** HMG; Menopur; Pergonal†; ***Swed.:*** Menopur; ***Switz.:*** Menogon†; Menopur; Merional; Pergonal†; ***Thai.:*** IVF-M; Menogon; ***Turk.:*** Menogon; Pergonal; ***UK:*** Menogon†; Menopur; Merional; ***USA:*** Humegon; Menopur; Pergonal†; Repronex; ***Venez.:*** Pergonal†.

Hydroxyestrone Diacetate

Hidroxiestrona, diacetato de; 16α-Hydroxyoestrone Diacetate. 3,16α-Dihydroxyestra-1,3,5(10)-trien-17-one diacetate.

$C_{22}H_{26}O_5$ = 370.4.

CAS — 566-76-7 (hydroxyestrone); 1247-71-8 (hydroxyestrone diacetate).



(hydroxyestrone)

Profile

Hydroxyestrone diacetate is an oestrogen (see Estradiol, p.2097). It has been given in vulvovaginal disorders and for female infertility.

Hydroxyprogesterone Caproate *(BANM, rINN)*

17-AHPC; Caproate d'hydroxyprogestirone; Caproato de hidroxiprogesterona; Hidroksiprogesteron Heksanoat; Hidroksiprogesteron Kaproat; Hydroxyprogesterone Hexanoate; Hydroxyprogesteroni Caproas; NSC-17592. 3,20-Dioxopregn-4-en-17α-yl hexanoate; 17α-Hydroxypregn-4-ene-3,20-dione hexanoate.

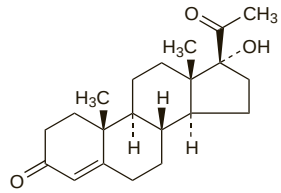
Гидроксипрогестерона Капроат

$C_{27}H_{40}O_4$ = 428.6.

CAS — 68-96-2 (hydroxyprogesterone); 630-56-8 (hydroxyprogesterone caproate).

ATC — G03DA03.

ATC Vet — QG03DA03.



(hydroxyprogesterone)

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Hydroxyprogesterone Caproate). A white or creamy-white, crystalline powder. Odourless or having a slight odour. Insoluble in water; soluble in ether; slightly soluble in benzene. Protect from light. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

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

There may be local reactions at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may occur during or immediately after injection of hydroxyprogesterone caproate but can be avoided by injecting the drug very slowly.

Pregnancy. Abnormalities reported in infants born to mothers who had received hydroxyprogesterone during pregnancy have included tetralogy of Fallot in one infant,[1] genito-urinary abnormalities in 2 infants,[2] and adrenocortical carcinoma in one infant.[3]

1. Heinonen OP, *et al*. Cardiovascular birth defects and antenatal exposure to female sex hormones. *N Engl J Med* 1977; **296:** 67–70.
2. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; **224:** 315–19.
3. Mann JR, *et al*. Transplacental carcinogenesis (adrenocortical carcinoma) associated with hydroxyprogesterone hexanoate. *Lancet* 1983; **ii:** 580.

Interactions

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

Uses and Administration

Hydroxyprogesterone caproate is a progestogen structurally related to progesterone (p.2125) that has been used for recurrent miscarriage and various menstrual disorders. In recurrent miscarriage associated with proven progesterone deficiency, doses of 250 to 500 mg weekly by intramuscular injection have been given during the first half of pregnancy. Hydroxyprogesterone caproate has also been used to prevent premature labour (see below).

The acetate and the enantate have also been used.

Premature labour. In women who have a history of spontaneous premature delivery (p.2003), there is some evidence to suggest that prophylactic progesterone, may reduce the risk for premature delivery in subsequent pregnancies. A placebo-controlled study[1] has used intramuscular injections of hydroxyprogesterone caproate, starting in weeks 16 to 20 of gestation and continuing until delivery or week 36. The risk of delivery at less than 37 weeks was reduced in women given hydroxyprogesterone, but the rate was still high at 36.3% of 306 women compared with 54.9% of 153 given placebo. Vaginal progesterone has been found to reduce the frequency of uterine contractions and the rate of preterm delivery in women at high risk,[2] and to reduce preterm delivery in women with a short cervix at mid-gestation.[3] The best timing of therapy is unclear, although two retrospective analyses[4,5] found that rates of preterm delivery were similar for two groups of women started on hydroxyprogesterone prophylaxis at either 16 to 20.9 weeks of gestation or 21 to 26.9 weeks. Another retrospective study[6] suggested that early cessation of hydroxyprogesterone was associated with an increased risk of spontaneous recurrent preterm delivery and that treatment should continue until 36 weeks of gestation.

Systematic reviews[7,8] of studies using progestogens (mainly hydroxyprogesterone) have concluded that prophylaxis does reduce the risk of preterm delivery and low birth-weight (less than 2.5 kg). However, further study is required, particularly to identify the optimal timing, route, and dose of treatment, and long-term effects on infant health.[8] Based on limited data, an expert committee in the USA has recommended[9] that the use of progesterone and hydroxyprogesterone should be restricted to women with a history of previous spontaneous delivery at less than 37