

PRODUCT INFORMATION

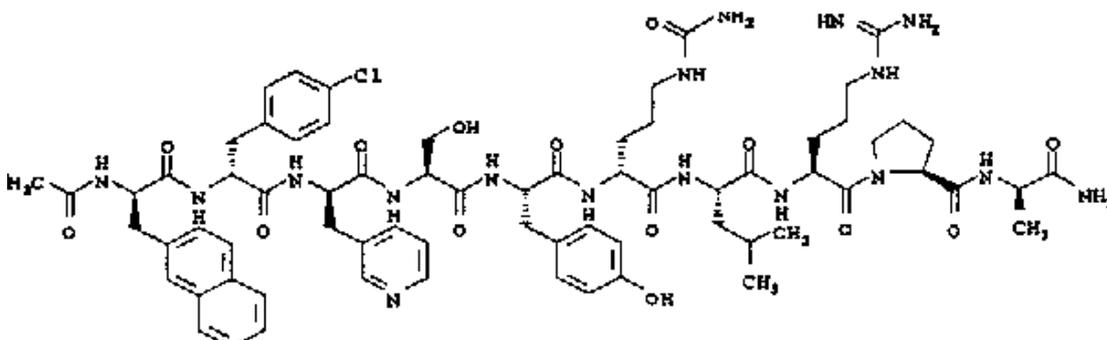
CETROTIDE® Cetorelix (as acetate)

NAME OF THE MEDICINE

CETROTIDE 250 microgram powder for injection vial with diluent syringe. The active ingredient in CETROTIDE is cetorelix, present as cetorelix acetate.

Cetorelix acetate is the acetate salt of a decapeptide with a sequence derived from luteinising hormone releasing hormone (LHRH) and subsequently modified. Five of the ten amino acids present are in the D configuration. The peptide is protected from degradation by means of C- and N-terminal protective groups (acetyl and amide protection). The peptide sequence and chemical structure are as follows:

Ac-D-Nal-D-p-Cl-Phe-D-Pal-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH₂



The molecular formula is C₇₀H₉₂ClN₁₇O₁₄ and the molecular weight is 1431.06. The CAS number is 130143-01-0.

DESCRIPTION

Cetorelix acetate is an amorphous white powder, moderately soluble in water and poorly soluble in organic solvents.

CETROTIDE is a lyophilised powder for injection. The powder contains mannitol as excipient. The packs also contain solvent (Water for Injections) in pre-filled syringes.

PHARMACOLOGY

Pharmacotherapeutic group: LHRH antagonist, ATC code: H01CC02.

Cetorelix is a LHRH antagonist. LHRH binds to membrane receptors on pituitary cells. Cetorelix competes with the binding of endogenous LHRH to these receptors.

Due to this mode of action, cetorelix controls the secretion of the gonadotrophins luteinising hormone (LH) and follicle stimulating hormone (FSH).

Cetorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation, the duration of action of cetorelix is dose dependent. Following a single dose of 3 mg of cetorelix, a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 250 microgram per injection, repeated injections every 24 hours will maintain the effect of cetorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetorelix were fully reversible after termination of treatment.

Pharmacokinetics

The absolute bioavailability of cetorelix after subcutaneous (s.c.) administration is about 85%.

The total plasma clearance and the renal clearance are 1.2 mL/min/kg and 0.1 mL/min/kg, respectively. The volume of distribution ($V_{d,area}$) is 1.1 L/kg. The mean terminal half-lives following intravenous (i.v.) and s.c. administration are about 12 hours and 30 hours, respectively, demonstrating the effect of absorption processes at the injection site. The s.c. administration of single doses (250 microgram to 3 mg cetorelix) and also daily dosing over 14 days show linear kinetics.

CLINICAL TRIALS

The efficacy and safety of cetorelix in controlled ovarian stimulation (COS) followed by assisted reproductive techniques was studied in 6 phase II and 3 phase III studies (total 884 patients). There were three pivotal phase III trials: the first trial was an open randomised controlled trial of cetorelix 250 microgram per day and the LHRH agonist buserelin, both used with human menopausal gonadotrophin (HMG). One hundred and eighty eight patients were treated with cetorelix and 86 with buserelin. The second trial was an open uncontrolled study also of cetorelix 250 microgram per day, in 346 patients. The third study was an open randomised controlled study including cetorelix 3 mg single dose and the LHRH agonist triptorelin; 115 patients were treated with cetorelix and 39 with triptorelin.

All studies enrolled women aged 18-39 years with normal uterus and without abnormal ovarian or menstrual function. In the single dose study, the primary efficacy endpoint was defined as prevention of premature LH surge that might have led to termination of the COS cycle. In the multiple dose studies, the primary endpoint was whether or not triggering with human chorionic gonadotrophin (HCG) was performed. Other parameters evaluated included HMG dose, egg numbers, ovum pick-up (OPU), embryo transfer (ET) and pregnancy rates.

The studies concluded that both cetrorelix dosage regimens effectively prevented premature ovulation and luteinisation when used with gonadotrophins in controlled ovarian stimulation, and were comparable to the LHRH agonists tested in this and other ART treatment outcome parameters evaluated.

INDICATIONS

Prevention of premature luteinisation and ovulation in patients undergoing a controlled ovarian stimulation followed by oocyte pick up and assisted reproductive techniques.

In clinical trials CETROTIDE was used with human menopausal gonadotrophin (HMG), however limited experience with recombinant FSH suggested similar efficacy.

CONTRAINDICATIONS

- Hypersensitivity to cetrorelix acetate or any structural analogues of GnRH, extrinsic peptide hormones or mannitol
- Pregnancy and lactation
- Post menopausal women
- Patients with moderate and severe renal and hepatic impairment

PRECAUTIONS

Luteal phase support should be given according to the reproductive medical centre's practice.

Ovarian Hyperstimulation Syndrome (OHSS)

During or following ovarian stimulation, ovarian hyperstimulation syndrome (OHSS) can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotrophins.

As OHSS can be life-threatening, the condition should be managed by a specialist experienced in the field.

Hypersensitivity

Caution is advised in patients with hypersensitivity to GnRH. Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. The treatment with Cetrotide is not advised in women with severe allergic conditions.

Repeated Ovarian Stimulation Cycles

There is limited experience up to now with the administration of CETROTIDE during a repeated ovarian stimulation procedure. Therefore CETROTIDE should be used in repeated cycles only after a careful risk/benefit evaluation.

Congenital Anomalies

The prevalence of congenital anomalies after the use of assisted reproductive technologies (ART) with or without GnRH antagonists may be slightly higher than after spontaneous conceptions although it is unclear whether this is related to factors inherent to the couple's infertility or the ART procedures.

Use in Pregnancy

(Category D).

CETROTIDE is not intended to be used during pregnancy (see CONTRAINDICATIONS). There is a theoretical risk of abortion if gonadotrophin releasing hormone antagonists are used during pregnancy. Studies in animals have indicated that cetorelix increased the incidence of total foetal resorptions when administered to pregnant rats and rabbits during the period of organogenesis, at respective subcutaneous doses of 14.7 microgram/kg/day and 6.8 microgram/kg/day. Cetorelix was not teratogenic in rats or rabbits at doses adversely affecting pregnancy.

Use in Lactation

CETROTIDE is not intended for use during lactation (see CONTRAINDICATIONS). It is not known whether, or to what extent, cetorelix is excreted into normal animal or human breast milk. Potential effects of cetorelix on breastfed infants have not been determined and CETROTIDE should, therefore, not be used in breastfeeding women.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long term carcinogenicity studies with cetorelix have not been carried out. Cetorelix showed no evidence of genotoxicity in assays for gene mutation in bacterial or mammalian cells. Tests for chromosomal damage in human lymphocytes *in vitro* and for micronucleus formation in mice *in vivo* showed that cetorelix was not clastogenic. Cetorelix induced binucleated cells and polyploidy in a strain of Chinese hamster lung cells *in vitro*, but this effect was not seen in human lymphocytes *in vitro* or in mouse bone marrow cells *in vivo*.

Cetorelix treatment resulted in a reversible cessation of mating in female rats at a subcutaneous dose of 464 microgram/kg/day and a reversible decrease in fertility in males at a dose of 68 microgram/kg/day. These are expected pharmacological effects of this class of drug.

Effects on Ability to Drive and Use Machines

Due to its pharmacological profile cetorelix is unlikely to impair the patient's ability to drive or to operate machinery.

INTERACTIONS WITH OTHER MEDICINES

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

ADVERSE EFFECTS

The safety of CETROTIDE in patients undergoing controlled ovarian stimulation was evaluated in 9 clinical studies. CETROTIDE was given in doses ranging from 0.1 mg to 5 mg, as either a single or multiple dose(s).

The following table shows systemic adverse events from the beginning of CETROTIDE treatment until the day of embryo transfer at an incidence of $\geq 1\%$.

	Cetrorelix Schedule		Reference Treatment	
	Multiple Dose Studies ≤ 0.5 mg/day n = 635	Single Dose Studies 3-5 mg/inj n = 187	Multiple Dose Studies n = 86	Single Dose Studies n = 39
Genitourinary: Ovarian Disorder	28 (4.4%)	4 (2.1%)	7 (8.1%)	3 (7.7%)
Neurological: Headache	8 (1.3%)	0 (0.0%)	7 (8.1%)	1 (2.6%)
Gastrointestinal: Nausea	8 (1.3%)	2 (1.1%)	1 (1.2%)	0 (0.0%)

Local reactions at the injection site (e.g. erythema, bruising, itching, swelling and pruritus) were reported. Usually, they were of transient nature and mild intensity. In very rare cases, general reactions have been reported.

A single case of hot flushes with a causality assessment of “likely” was also recorded during treatment with cetrorelix in clinical trials.

A severe hypersensitivity reaction, associated with cough, rash and hypotension, was observed in one patient after 7 months of treatment of ovarian cancer with cetrorelix (10 mg/day). The patient recovered completely within 20 minutes. A causal relationship could not be excluded.

The following definitions apply to the frequency terminology used hereafter:

Very Common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1,000$
Very Rare	$< 1/10,000$

Immune system disorders

Uncommon: Systemic allergic/ pseudo-allergic reactions including life-threatening anaphylaxis

Nervous system disorders

Uncommon: Headache

Gastrointestinal disorders

Uncommon: Nausea

Reproductive system and breast disorders

Common: Mild to moderate ovarian hyperstimulation syndrome (WHO grade I or II) can occur which is an intrinsic risk of the stimulation procedure.

Uncommon: Severe ovarian hyperstimulation syndrome (WHO grade III)

General disorders and administration site conditions

Common: Local reactions at the injection site (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

DOSAGE AND ADMINISTRATION

CETROTIDE should only be prescribed by or under the supervision of a specialist experienced in this field.

CETROTIDE is for subcutaneous injection into the lower abdominal wall.

The first administration of CETROTIDE should be performed under the supervision of a physician. It is advised that the patient be kept under medical supervision for 30 minutes to ensure there is no allergic/pseudo-allergic reaction to the injection. Facilities for the treatment of such reactions should be immediately available.

Subsequent injections with CETROTIDE may be self-administered as long as the patient is made aware of the signs and symptoms that may include hypersensitivity, the consequences of such a reaction and the need for immediate intervention.

The contents of 1 vial of CETROTIDE 250 microgram are to be administered once daily, at 24-hour intervals, either in the morning or in the evening.

Administration in the morning: Treatment with CETROTIDE 250 microgram should commence on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or recombinant gonadotrophins and is to be continued throughout the gonadotrophin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with CETROTIDE 250 microgram should commence on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotrophins and is to be continued throughout the gonadotrophin treatment period until the evening prior to the day of ovulation induction.

Preparation for Administration

As cetrotirelix is incompatible with several ingredients of common parenteral solutions, it should be dissolved only by using Water for Injections.

CETROTIDE should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 230 microgram cetrotirelix (250 microgram strength).

The solution should be used immediately after reconstitution.

Use in one patient on one occasion only. CETROTIDE contains no antimicrobial preservative.

The injection site should be varied daily.

OVERDOSAGE

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents, non-specific toxic symptoms were observed after intraperitoneal administration of cetrotirelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

Advise your patients to immediately contact their doctor or the Poisons Information Centre (in Australia telephone 131 126, in New Zealand telephone 0800 764 766) if they are concerned that they have given themselves too much CETROTIDE.

PRESENTATION AND STORAGE CONDITIONS

Store below 25°C. Protect from light.

PRESENTATION

Packs with 1 or 7 Type 1 glass vials, each containing cetrotirelix 250 microgram (as cetrotirelix acetate) powder for injection, sealed with a rubber stopper.

In addition, for each vial the packs contain:

- 1 pre-filled syringe (Type 1 glass cartridge closed with rubber stoppers) with 1 mL solvent for parenteral use (Water for Injections)
- 1 injection needle (20 gauge)
- 1 hypodermic injection needle (27 gauge)
- 2 alcohol swabs

After reconstitution with the solvent provided, the concentration of cetorelix is 250 microgram/mL.

NAME AND ADDRESS OF THE SPONSOR

CETROTIDE is supplied in Australia by:

Merck Serono Australia Pty Ltd
3-4/25 Frenchs Forest Rd
Frenchs Forest NSW 2086

CETROTIDE is supplied in New Zealand by:

Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks, Auckland

POISON SCHEDULE OF THE MEDICINE

Schedule 4

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 19 December 2000

Date of most recent amendment: 9 August 2017

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