NEW ZEALAND DATA SHEET

1 PRODUCT NAME

CETROTIDE® 250 microgram powder for injection vial with diluent syringe.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 microgram of cetrorelix (as acetate). After reconstitution with the solvent provided, the concentration of cetrorelix is 250 microgram/mL.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Cetrorelix 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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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 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 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 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 cetrorelix 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 210 microgram cetrorelix. Each vial contains 250 microgram of cetrorelix; however, due to losses during reconstitution and administration, only 210 microgram can be administered.

The solution should be used immediately after reconstitution.

Use in one patient on one occasion only. CETROTIDE contains no anti-microbial preservative

The injection site should be varied daily.

4.3 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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Cetrorelix 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.

See Section 5.3 PRECLINICAL SAFETY DATA.

Use in pregnancy

Category D

CETROTIDE is not intended to be used during pregnancy (see Section 4.3 CONTRAINDICATIONS). There is a theoretical risk of abortion if gonadotrophin releasing hormone antagonists are used during pregnancy. Studies in animals have indicated that cetrorelix 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. Cetrorelix was not teratogenic in rats or rabbits at doses adversely affecting pregnancy.

Use in lactation

CETROTIDE is not intended for use during lactation (see Section 4.3 CONTRAINDICATIONS). It is not known whether, or to what extent, cetrorelix is excreted into normal animal or human breast milk. Potential effects of cetrorelix on breastfed infants have not been determined and CETROTIDE should, therefore, not be used in breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 ≥ 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	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems in Australia, or at https://pophealth.my.site.com/carmreportnz/s/ in New Zealand.

4.9 OVERDOSE

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 cetrorelix 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) if they are concerned that they have given themselves too much CETROTIDE.

For risk assessment and advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766) in New Zealand.

5 PHARMACOLOGICAL PROPERTIES

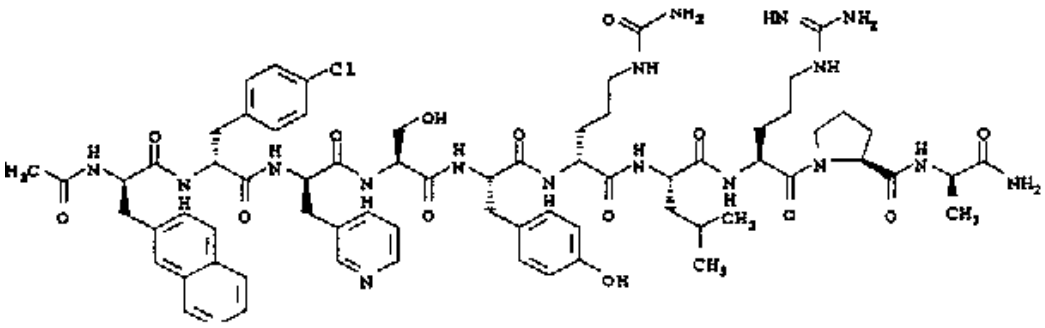
5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: LHRH antagonist, ATC code: H01CC02.

Chemical structure

Cetrorelix 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-NH_2



The molecular formula is $C_{70}H_{92}ClN_{17}O_{14}$ and the molecular weight is 1431.06.

CAS number

130143-01-0

Mechanism of action

Cetrorelix is a LHRH antagonist. LHRH binds to membrane receptors on pituitary cells. Cetrorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetrorelix controls the secretion of the gonadotrophins luteinising hormone (LH) and follicle stimulating hormone (FSH).

Cetrorelix 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, cetrorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation, the duration of action of cetrorelix is dose dependent. Following a single dose of 3 mg of cetrorelix, 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 vial, repeated injections every 24 hour will maintain the effect of cetrorelix.

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

Clinical trials

The efficacy and safety of cetrorelix 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 cetrorelix 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 cetrorelix and 86 with buserelin. The second trial was an open uncontrolled study also of cetrorelix 250 microgram per day, in 346 patients. The third study was an open randomised controlled study including cetrorelix 3 mg single dose and the LHRH agonist triptorelin; 115 patients were treated with cetrorelix 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.

5.2 PHARMACOKINETIC PROPERTIES

The absolute bioavailability of cetrorelix 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 cetrorelix) and also daily dosing over 14 days show linear kinetics.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cetrorelix 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 cetrorelix was not clastogenic. Cetrorelix 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*.

Carcinogenicity

Long term carcinogenicity studies with cetrorelix have not been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder: Mannitol

Solvent: Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

24 months

Information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG) in Australia or on Medsafe Product Detail in New Zealand. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze).

For patients: Should refrigeration be unavailable, CETROTIDE can be stored below 30°C for a single period of up to 3 months after which it must be discarded.

Store in the original package in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Packs with 1 or 7* Type 1 glass vials, each containing cetrorelix 250 microgram (as cetrorelix 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)

*Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

CETROTIDE is supplied in Australia by:

Merck Healthcare Pty Ltd

Suite 1, Level 1, Building B

11 Talavera Road

Macquarie Park NSW 2113

E-mail: medinfo.australia@merckgroup.com

Phone: 1800 633 463

CETROTIDE is supplied in New Zealand by:

Healthcare Logistics

58 Richard Pearse Drive

Airport Oaks, Auckland

E-mail: medinfo.australia@merckgroup.com

Phone: 0800 426 252

9 DATE OF FIRST APPROVAL

24 May 2000

10 DATE OF REVISION OF THE TEXT

12 Nov 2025

Summary table of changes

Section changes	Summary
4.2	Correction of the actual delivered dose Included additional note regarding the delivered dose after reconstitution and administration.
4.8	Updated the adverse reactions reporting webpage for New Zealand.
4.9	Updated information to include risk assessment wording
5.1	Included Chemical structure and CAS number Rephrased the text from injection to vial based on the product's strength