

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrCetrotide®

Cetrorelix for Injection

0.25 mg cetrorelix (as cetrorelix acetate)
Powder for Solution, Subcutaneous

GnRH antagonist

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PrCetrotide®
Cetrotide for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CETROTIDE® (cetrotide for injection) is indicated for the prevention of premature ovulation in patients undergoing controlled ovarian stimulation.

2 CONTRAINDICATIONS

CETROTIDE (cetrotide for injection) is contraindicated under the following conditions:

- Hypersensitivity to cetrotide acetate, extrinsic peptide hormones, mannitol, or any component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- Known hypersensitivity to GnRH or any other GnRH analogs.
- Known or suspected pregnancy, and lactation (see PRECAUTIONS).
- Moderate or severe impairment of hepatic or renal function.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

Ovarian stimulation therapy with gonadotropins (FSH, hMG) is started on cycle Day 2 or 3. The dose of gonadotropins should be adjusted according to individual response. The response should be primarily based on the number and size of the developing follicles as evidenced by ultrasound. This may be more reliable than by the amount of circulating estradiol. CETROTIDE (cetrotide for injection) may be administered subcutaneously once daily (0.25 mg dose) as part of the multiple dose protocol during the early- to mid-follicular phase.

CETROTIDE (cetrotide for injection) 0.25 mg is administered on either stimulation day 5 (morning or evening) or day 6 (morning). It is administered once daily at the same time each day at 24 hour intervals and continued daily until the day of hCG administration.

When assessment by ultrasound shows a sufficient number of follicles of adequate size (≥ 17 mm in diameter), hCG is administered to induce ovulation and final maturation of the oocytes. No hCG should be administered if the ovaries show an excessive response to the treatment with gonadotropins to reduce the chance of developing ovarian hyperstimulation syndrome (OHSS).

3.2 Administration

The first administration of CETROTIDE (cetorelix for injection) 0.25 mg should be performed under the supervision of a physician and under conditions where treatment of possible allergic/pseudo-allergic reactions (including life-threatening anaphylaxis) is immediately available. The subsequent injections may be self-administered after appropriate instructions by the doctor as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention.

3.3 Reconstitution

Table 1 – Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
2 mL	1 mL	1.1 mL	0.25 mg

The reconstituted product is to be administered subcutaneously. Use immediately after reconstitution.

As with all parenteral drug products, reconstituted solutions should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portions.

3.4 Missed Dose

If you miss a dose of CETROTIDE (cetorelix for injection) do not double dose. Discuss with your doctor when you should receive your next dose. Check with your doctor if you have any questions about this.

4 OVERDOSAGE

There have been isolated reports of overdosage with CETROTIDE (cetorelix for injection) 0.25 mg in humans but no adverse events were reported. In addition, single doses up to 120 mg CETROTIDE (cetorelix for injection) have been well tolerated in patients treated for other indications without signs of overdosage.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Form, Strength, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	0.25 mg cetorelix (as cetorelix acetate), Powder for Solution	Mannitol

5.1 Composition

CETROTIDE (cetorelix for injection) 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, Ph.Eur, that comes supplied in a 1.0 mL (for 0.25 mg vial) pre-filled syringe. Each vial of CETROTIDE (cetorelix for injection) 0.25 mg (multiple dose regimen) contains 0.25 mg of cetorelix as cetorelix acetate and 54.80 mg of mannitol.

5.2 Dosage Forms and Packaging

CETROTIDE (cetorelix for injection) is supplied in a sterile, lyophilized form in a single dose vial containing cetorelix acetate.

CETROTIDE (cetorelix for injection) 0.25 mg is available in a carton of one packaged tray. Each packaged tray contains: one glass vial containing 0.25 mg of cetorelix base, one pre-filled glass syringe with 1 mL of Sterile Water for Injection, Ph.Eur., one 20 gauge needle (yellow), one 27 gauge needle (grey), and two alcohol swabs. After reconstitution with the solvent provided, each mL of solution contains 0.25 mg cetorelix (base).

The reconstituted product is to be administered by subcutaneous injection only.

CETROTIDE (cetorelix for injection) does not contain latex.

6 WARNINGS AND PRECAUTIONS

General

CETROTIDE (cetorelix for injection) should be prescribed by physicians who are experienced in fertility treatment. Before starting treatment with CETROTIDE (cetorelix for injection), pregnancy must be excluded (see CONTRAINDICATIONS).

Prior to therapy with CETROTIDE (cetorelix for injection), patients should be informed of the duration of treatment and monitoring procedures that will be required. The risk of possible adverse reactions should be discussed (see ADVERSE REACTIONS). CETROTIDE (cetorelix for injection) should not be prescribed if a patient is pregnant. If CETROTIDE (cetorelix for injection) is prescribed to patients for self-administration, information for proper use is given in the Patient Insert (see CONSUMER INFORMATION).

Carcinogenesis and Mutagenesis

Long-term carcinogenicity studies in animals have not been performed with cetrorelix acetate. Cetrorelix acetate was not genotoxic in vitro (Ames test, HPRT test, chromosome aberration test) or in vivo (chromosome aberration test, mouse micronucleus test). Cetrorelix acetate induced polyploidy in CHL-Chinese hamster lung fibroblasts, but not in V79-Chinese hamster lung fibroblasts, cultured peripheral human lymphocytes or in an in-vitro micronucleus test in the CHL-cell line.

Immune

Caution is advised in patients with hypersensitivity to GnRH analogs. These patients should be carefully monitored after the first injection, where treatment of possible allergic/pseudo-allergic reactions (including life-threatening anaphylaxis) is immediately available. Therefore, it is recommended that a physician supervises the first administration. Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with CETROTIDE (cetrorelix for injection), is not advised in women with severe allergic conditions.

Efficacy and safety (immunogenicity and/or sensitization) have not been extensively evaluated in women undergoing multiple treatment cycles with CETROTIDE (cetrorelix for injection). However, hypersensitivity, antibody formation, and acute anaphylactic reaction have been reported with GnRH analogs. Therefore, special care should be taken upon using the drug in the same patient for more than one cycle.

Sexual Function/Reproduction

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.

Ovarian Hyperstimulation Syndrome (OHSS):

During or following ovarian stimulation an ovarian hyperstimulation syndrome (OHSS) can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins. Protocols combining gonadotropins and GnRH antagonist have been found to be correlated with a shorter duration of stimulation and of lower dose of gonadotropins, lower estradiol level. These findings may account for the reduction of the risk of OHSS, associated with the use of GnRH antagonists.

Impairment of Fertility

Treatment with 0.46 mg/kg cetrorelix acetate for 4 weeks resulted in complete infertility in female rats which was reversed 8 weeks after cessation of treatment.

6.1 Special Populations

6.1.1 Pregnant Women

CETROTIDE (cetorelix for injection) is contraindicated in pregnant women.

When administered to rats for the first seven days of pregnancy, cetorelix acetate did not affect the development of the implanted conceptus at doses up to 38 µg/kg (approximately 1 times the recommended human therapeutic dose based on body surface area). However, a dose of 139 µg/kg (approximately 4 times the human dose) resulted in a resorption rate and a post-implantation loss of 100%.

When administered from day 6 to near term to pregnant rats and rabbits, very early resorptions and total implantation losses were seen in rats at doses from 4.6 µg /kg (0.2 times the human dose) and in rabbits at doses from 6.8 µg /kg (0.4 times the human dose). In animals that maintained their pregnancy, there was no increase in the incidence of fetal abnormalities.

The fetal resorption observed in animals is a logical consequence of the alteration in hormonal levels effected by the antigonadotrophic properties of CETROTIDE (cetorelix for injection), which could result in fetal loss in humans as well. Therefore, this drug should not be used in pregnant women.

6.1.2 Breast-feeding

It is not known whether CETROTIDE (cetorelix for injection) is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of CETROTIDE (cetorelix for injection) on lactation and/or the breast-fed child have not been determined, CETROTIDE (cetorelix for injection) is contraindicated for nursing mothers.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The safety of CETROTIDE (cetorelix for injection) in 949 patients undergoing controlled ovarian stimulation in clinical studies was evaluated. Women were between 19 and 40 years of age (mean: 32). 94.0 % of them were Caucasian. CETROTIDE (cetorelix for injection) was given in doses ranging from 0.1 mg to 5 mg as either a single or multiple dose.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 3 – Adverse Events in Patients in Controlled Ovarian Stimulation Clinical Studies

Adverse Event (WHO preferred term)	CETROTIDE (cetorelix for injection) N=949 % (n)
Ovarian Hyperstimulation Syndrome Mild to Moderate (WHO grade I and II) Severe (WHO grade III)	5.7 (54) 0.53 (5)
Nausea	1.3 (12)
Headache	1.1 (10)

Table 3 shows systemic adverse events from the beginning of CETROTIDE (cetorelix for injection) treatment until confirmation of pregnancy by ultrasound in CETROTIDE (cetorelix for injection) treated subjects undergoing COS (Controlled Ovarian Stimulation).

Local site reactions (e.g. pain, redness, swelling pruritus, erythema, hematoma and/or irritation at the site of injection) have been commonly reported. Usually, they were of a transient nature and mild intensity. Uncommon cases of systematic allergic/pseudo-allergic reactions including life-threatening anaphylactoid reactions have been observed.

Two stillbirths were reported in Phase 3 studies of CETROTIDE (cetorelix for injection).

Ovarian Hyperstimulation Syndrome (OHSS)

During or following controlled ovarian stimulation it is common for mild to moderate ovarian hyperstimulation syndrome (WHO grade I or II) to occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins (refer to the relevant gonadotropin Product Monograph for warning symptoms etc.).

In this potentially serious medical event, the ovaries are massively enlarged, and intravascular fluid volume shifts into the peritoneal space, resulting in hypovolemia, oliguria, hemoconcentration, and massive ascites. The syndrome can usually be avoided by closely monitoring the patient and withholding the hCG if ovarian response becomes excessive.

Severe OHSS (WHO grade III) is uncommon.

Congenital Anomalies

Clinical follow-up studies of 316 newborns of women administered CETROTIDE (cetorelix for injection) were reviewed. One infant of a set of twin neonates was found to have anencephaly at birth and died after four days. The other twin was normal. Developmental findings from ongoing baby follow-up included a child with a ventricular septal defect and another child with bilateral congenital glaucoma.

Four pregnancies that resulted in therapeutic abortion in Phase 2 and Phase 3 controlled ovarian stimulation studies had major anomalies (diaphragmatic hernia, trisomy 21, Klinefelter syndrome, polymalformation, and trisomy 18). In three of these four cases, intracytoplasmic

sperm injection (ICSI) was the fertilization method employed; in the fourth case, in-vitro fertilization (IVF) was the method employed.

The minor congenital anomalies reported include: supernumerary nipple, bilateral strabismus, imperforate hymen, congenital nevi, hemangiomas, and QT syndrome.

The causal relationship between the reported anomalies and CETROTIDE (cetorelix for injection) is unknown. Multiple factors, genetic and others (including, but not limited to ICSI, IVF, gonadotropins, and progesterone) make causal attribution difficult to study.

8 DRUG INTERACTIONS

8.1 Drug-Drug Interactions

No formal drug interaction studies have been performed with CETROTIDE (cetorelix for injection). In clinical studies, no interaction between exogenous gonadotropins and CETROTIDE (cetorelix for injection) was observed.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

CETROTIDE (cetorelix for injection) is a synthetic decapeptide with gonadotropin-releasing hormone (GnRH) antagonistic activity. Cetorelix acetate is an analog of native GnRH with substitutions of amino acids at positions 1, 2, 3, 6, and 10. The molecular formula is Acetyl-*D*-3-(2'-naphthyl)-alanine-*D*-4-chlorophenylalanine-*D*-3-(3'-pyridyl)-alanine-*L*-serine-*L*-tyrosine-*D*-citruiline-*L*-leucine-*L*-arginine-*L*-proline-*D*-alanine-amide, and the molecular weight is 1431.06, calculated as the anhydrous free base.

GnRH induces the production and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the gonadotrophic cells of the anterior pituitary. Due to a positive estradiol (E₂) feedback at midcycle, GnRH liberation is enhanced resulting in an LH-surge. This LH-surge induces the ovulation of the dominant follicle, resumption of oocyte meiosis and subsequently luteinization as indicated by rising progesterone levels.

CETROTIDE (cetorelix for injection) competes with natural GnRH for binding to membrane receptors on pituitary cells and thus controls the release of LH and FSH in a dose-dependent manner. The onset of LH suppression is approximately two hours with the 0.25 mg dose. This suppression is maintained by continuous treatment and there is a more pronounced effect on LH than on FSH. An initial release of endogenous gonadotropins has not been detected with CETROTIDE (cetorelix for injection), which is consistent with an antagonist effect.

The effects of CETROTIDE (cetorelix for injection) on LH and FSH are reversible after discontinuation of treatment. In women, CETROTIDE (cetorelix for injection) delays the LH-surge, and consequently ovulation, in a dose-dependent fashion. FSH levels are not affected at the doses used during controlled ovarian stimulation. A dose of CETROTIDE (cetorelix for injection) 0.25 mg every 24 hours has been shown to maintain the effect.

9.2 Pharmacodynamics

Human:

GnRH induces the production and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the gonadotrophic cells of the anterior pituitary. Due to a positive estradiol (E₂) feedback at midcycle, GnRH liberation is enhanced resulting in an LH-surge. This LH-surge induces the ovulation of the dominant follicle, resumption of oocyte meiosis and subsequently luteinization as indicated by rising progesterone levels.

CETROTIDE (cetorelix for injection) competes with natural GnRH for binding to membrane receptors on pituitary cells and thus controls the release of LH and FSH in a dose-dependent manner. The onset of LH suppression is approximately one hour with the 3 mg dose and two hours with the 0.25 mg dose. This suppression is maintained by continuous treatment and there is a more pronounced effect on LH than on FSH. An initial release of endogenous gonadotropins has not been detected with CETROTIDE (cetorelix for injection), which is consistent with an antagonist effect.

The effects of CETROTIDE (cetorelix for injection) on LH and FSH are reversible after discontinuation of treatment. In women, CETROTIDE (cetorelix for injection) delays the LH-surge, and consequently ovulation, in a dose-dependent fashion. FSH levels are not affected at the doses used during controlled ovarian stimulation. Following a single 3 mg dose of CETROTIDE (cetorelix for injection), duration of action of at least 4 days has been established. A dose of CETROTIDE (cetorelix for injection) 0.25 mg every 24 hours has been shown to maintain the effect.

Animal:

The decapeptide Cetorelix (cetorelix acetate for injection) is characterised as a potent antagonist of LHRH in various *in vitro* and animal models. In the corresponding experiments it is shown that Cetorelix binds competitively and with high affinity to pituitary LHRH-receptors and thereby induces a strong and dose dependent suppression of gonadotropin and subsequently sex-steroid secretion. Corresponding to this completely different mode of action as compared to LHRH-agonists, the hormone-suppression is induced within a few hours after the start of treatment with Cetorelix and thus avoids the "flare-up effect". On the other hand, administration of an LHRH-agonist can override the suppressive effects of an antagonist, indicating the competitive binding of Cetorelix to pituitary receptors.

Due to the hormone-withdrawal induced by sufficiently high doses, a cessation of reproductive function in female and male animals is observed, which is reversible after treatment termination. The pharmacological principle of hormone suppression is also demonstrated by the growth-inhibition and regression of hormone-sensitive tumors of different histological types. During prolonged daily therapy over a period of 16 weeks no escape from tumor growth inhibition was observed and after initial high dose treatment, a reduced maintenance dose was fully active. Due to the high stability of the Cetorelix molecule as compared to natural LHRH, there is a prolonged elimination half-life of active compound after subcutaneous administration, which is a prerequisite for a prolonged duration of action. This assumption is supported by the fact that the main metabolite of Cetorelix in rat bile has no pharmacological activity.

The presence of LHRH receptors was also demonstrated in a variety of benign and malignant tissues and therefore might form the basis for hormone-independent effects, although the concentration needed for such effects are far above those necessary for hormone suppression. Therefore, it is unlikely that Cetrorelix treatment, in doses sufficient to suppress the pituitary gonadotropins, has any relevant influence on the physiological function of other LHRH-receptor bearing cells. In addition, it was found that Cetrorelix has a high receptor-specificity, since it does not bind to other receptors of this receptor-family.

In safety pharmacological studies Cetrorelix showed a very favourable profile. In contrast to former antagonists, Cetrorelix did not exert histamine-related side effects. Neither anaphylactoid reactions, nor adverse effects on cardio-vascular, respiratory, CNS, renal, hepatic and gastro-intestinal functions were observed. Based on these findings Cetrorelix has a positive risk-benefit ratio with respect to its clinical use.

9.3 Pharmacokinetics

Human:

The pharmacokinetic parameters of single and multiple doses of CETROTIDE (cetrorelix for injection) in adult healthy female subjects are summarized in Table 4.

Table 4 – Summary of Pharmacokinetic parameters of CETROTIDE (cetrorelix for injection) following 3 mg single or 0.25 mg single and multiple (daily for 14 days) subcutaneous (sc) administration

	Single dose 3 mg	Single dose 0.25 mg	Multiple dose 0.25 mg
No. of subjects	12	12	12
t _{max} * [h]	1.5 (0.5 – 2)	1.0 (0.5 – 1.5)	1.0 (0.5 – 2)
t _{1/2} * [h]	62.8 (38.2 – 108)	5.0 (2.4 – 48.8)	20.6 (4.1 – 179.3)
C _{max} [ng/ml]	28.5 (22.5 – 36.2)	4.97 (4.17 – 5.92)	6.42 (5.18 – 7.96)
AUC [ng•h/ml]	536 (451 – 636)	31.4 (23.4 – 42.0)	44.5 (36.7 – 54.2)
CL [†] [ml/min•kg]	1.28 ^a		
V _z [†] [l/kg]	1.16 ^a		

Geometric mean (95%CI_{ln}), [†]arithmetic mean, or * median (min-max)

- t_{max} Time to reach observed maximum plasma concentration
- t_{1/2} Elimination half-life
- C_{max} Maximum plasma concentration; multiple dose C_{ss, max}
- AUC Area under the curve; single dose AUC_{0-inf}, multiple dose AUC_τ
- CL Total plasma clearance
- V_z Volume of distribution
- ^a Based on iv administration (n=6, separate study 0013)

Absorption: CETROTIDE (cetorelix for injection) is rapidly absorbed following subcutaneous injection, maximal plasma concentrations being achieved approximately one to two hours after administration. The mean absolute bioavailability of CETROTIDE (cetorelix for injection) following subcutaneous administration to healthy female subjects is 85%.

Distribution: The volume of distribution of CETROTIDE (cetorelix for injection) following a single intravenous dose of 3 mg is about 1 L/kg. *In vitro* protein binding to human plasma is 86%.

CETROTIDE (cetorelix for injection) concentrations in follicular fluid and plasma were similar on the day of oocyte pick-up in patients undergoing controlled ovarian stimulation. Following subcutaneous administration of CETROTIDE (cetorelix for injection) 0.25 mg and 3 mg, plasma concentrations of cetorelix were below or in the range of the lower limit of quantitation on the day of oocyte pick up and embryo transfer.

Metabolism: After subcutaneous administration of 10 mg CETROTIDE (cetorelix for injection) to females and males, CETROTIDE (cetorelix for injection) and small amounts of (1-9), (1-7), (1-6), and (1-4) peptides were found in bile samples over 24 hours.

In *in vitro* studies, CETROTIDE (cetorelix for injection) was stable against phase I- and phase II-metabolism. CETROTIDE (cetorelix for injection) was transformed by peptidases, and the (1-4) peptide was the predominant metabolite.

Excretion: Following subcutaneous administration of 10 mg cetorelix to males and females, only unchanged cetorelix was detected in urine. In 24 hours, cetorelix and small amounts of the (1-9), (1-7), (1-6), and (1-4) peptides were found in bile samples. 2-4% of the dose was eliminated in the urine as unchanged cetorelix, while 5-10% was eliminated as cetorelix and the four metabolites in bile. Therefore, only 7-14% of the total dose was recovered as unchanged cetorelix and metabolites in urine and bile up to 24 hours. The remaining portion of the dose may not have been recovered since bile and urine were not collected for a longer period of time.

Animal:

Absorption: Both differently radiolabelled peptides were absorbed rapidly and completely by rats and dogs following a single sc administration of 0.1 mg/kg. The absolute bioavailability following sc administration is about 100 % in rats and dogs and a dose proportionality can be observed with regard to AUC in a dose range of 0.02 to 0.5 mg/kg.

Distribution: Distribution of cetorelix is rapid. Maximum [¹⁴C] tissue levels could be mostly measured in the first hours after administration. Target organs of the Arg-label as well as of the D-Phe-label are the organs of elimination and excretion (kidney, liver, intestine) and the organs containing LHRH binding sites (pituitary gland, ovaries, adrenals). Due to metabolisation the long terminal half lives ($t_{1/2}$) of the Arg-label in plasma and organs did not reflect the behaviour of cetorelix itself as proven by investigations with the D-Phe-label.

Metabolism: Metabolic investigations (*in vivo*) using the Arg-label show that the peptide is degraded by endo- or exopeptidases. The radiolabelled amino acid Arg is liberated and enters the metabolic pathways of the animal organism. This is the reason for the long $t_{1/2}$ in plasma and

organs, the excretion of radiolabelled urea in urine and the exhalation of [¹⁴C]CO₂. Administering the D-Phe-label, peptide fragments were detectable in bile and feces of rats and dogs. In urine only parent compound was excreted.

Excretion: The excretion balance of the D-Phe-label is about 100 % when collecting samples cumulative in one pot. Fractionated sampling of urine and feces lead to some loss of radiolabel which is possibly due to observed unspecific binding of the peptide to vessel surfaces but despite this effect the excretion balance of the D-Phe-label is >90 %.

Special Populations and Conditions

There is no evidence of differences in pharmacokinetic parameters for CETROTIDE (cetrotirelix for injection) between healthy subjects and patients undergoing controlled ovarian stimulation.

Pediatrics: Pharmacokinetic investigations have not been performed in children (see PRECAUTIONS).

Geriatrics: Pharmacokinetic investigations have not been performed in the elderly (see PRECAUTIONS).

Ethnic origin: Pharmacokinetic differences in different races have not been determined.

Hepatic Insufficiency: Pharmacokinetic investigations have not been performed in subjects with impaired liver function.

Renal Insufficiency: Pharmacokinetic investigations have not been performed in subjects with impaired renal function.

10 STORAGE, STABILITY AND DISPOSAL

Pharmacy/Clinic: Store at 2 - 8°C (in a refrigerator).

Patient: Store at 2 - 8°C (in a refrigerator). Storage at up to 30°C for a maximum of 3 months is allowed.

Do not freeze. Keep the container in the outer carton to protect it from light. Do not use the product after the expiry date indicated on the label.

The solution should be used immediately after preparation. Each vial and syringe should be used only once.

Store the medicine out of the reach of children.

11 SPECIAL HANDLING INSTRUCTIONS

Use the syringe and needles only once. Dispose of the syringe and needles immediately after use into your disposal container or puncture-proof container with a lid that fits firmly.

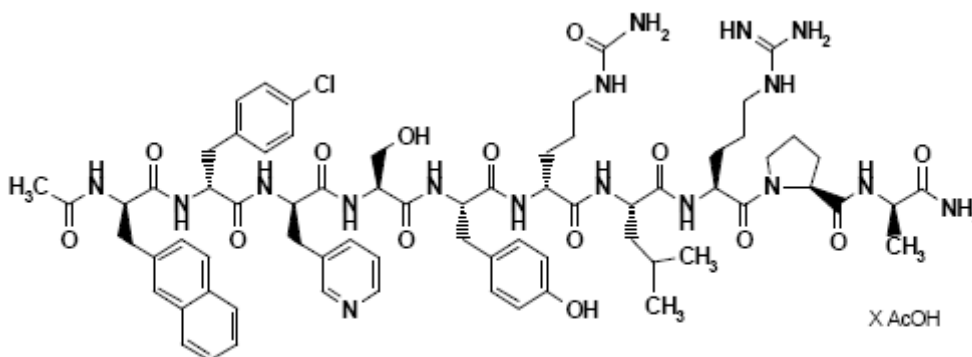
PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common name: Cetorelix Acetate
Chemical name: GnRH Antagonist
Molecular formula: Ac-D-Nal-D-p-Cl-Phe-D-Pal-ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH₂
Molecular weight: 1431.06 g/mol (base); 1490.11 g/mol (monoacetate);
1519.58 g/mol (as base x 1.5 acetate)

Structural formula:



Physicochemical properties:

Physical form: white powder

Solubility:

Water	8 mg/ml
Water/Mannitol	5 mg/ml
Acetic acid (30%)	50 mg/ml
Sodium phosphate buffer pH 7.4	1 mg/ml
Dichloromethane	Insoluble (<0.5 mg/ml)

Melting Point: 232.1 °C $\text{rsd} = \pm 0.69\%$ (n=6)

Polymorphism: amorphous (x-ray diffraction spectrum of cetorelix acetate reference standard – evidence of chemical structure)

pH: 5.6 (0.1 % in water)

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 5 – Summary of patient demographics for clinical trials in the prevention of premature ovulation in patients undergoing controlled ovarian stimulation

No. of Trials	Trial design	Dosage, route of administration and duration	Total Study subjects (n)	Mean age (Range)	Sex
2	Phase 2 (dose-finding)	3 mg, Single dose per treatment cycle, Subcutaneous	732	32 years	Females
1	Phase 3	3 mg, Single dose per treatment cycle, Subcutaneous			
2	Phase 3	0.25 mg, Multiple dosing per treatment cycle, Subcutaneous			

Seven hundred thirty two (732) patients were treated with CETROTIDE (cetorelix for injection) in five (two Phase 2 dose-finding and three Phase 3) clinical trials. The clinical trial population consisted of Caucasians (95.5%) and Black, Asian, Arabian and Others (4.5%). Women were between 19 and 40 years of age (mean: 32 years). The studies excluded subjects with polycystic ovary syndrome (PCOS), subjects with low or no ovarian reserve, and subjects with stage III-IV endometriosis.

Two dose regimens were investigated in these clinical trials, either a single dose per treatment cycle or multiple dosing. In the Phase 2 studies, a single dose of 3 mg was established as the minimal effective dose for the inhibition of premature LH surges with a protection period of at least 4 days. When CETROTIDE (cetorelix for injection) is administered in a multidose regimen, 0.25 mg was established as the minimal effective dose. The extent and duration of LH-suppression is dose dependent.

In the Phase 3 program, efficacy of the single 3 mg dose regimen of CETROTIDE (cetorelix for injection) and the multiple 0.25 mg dose regimen of CETROTIDE (cetorelix for injection) was established separately in two adequate and well controlled clinical studies utilizing active comparators. A third non-comparative clinical study evaluated only the multiple 0.25 mg dose regimen of CETROTIDE (cetorelix for injection). The ovarian stimulation treatment with recombinant FSH or human menopausal gonadotropin (hMG) was initiated on day 2 or 3 of a normal menstrual cycle. The dose of gonadotropins was administered according to the individual patient's disposition and response.

In the single dose regimen study, CETROTIDE (cetorelix for injection) 3 mg was administered on the day of controlled ovarian stimulation (COS) when adequate estradiol levels (400 pg/ml) were obtained, usually on day 7 (range day 5-12). If human chorionic gonadotropin (hCG) was not given within 4 days of the 3 mg dose of CETROTIDE (cetorelix for injection), then 0.25 mg of CETROTIDE (cetorelix for injection) was administered daily beginning 96 hours after the 3 mg injection until and including the day of hCG administration.

In the two multiple dose regimen studies, CETROTIDE (cetorelix for injection) 0.25 mg was started on day 5 or 6 of COS. Both gonadotropins and CETROTIDE (cetorelix for injection) were continued daily (multiple dose regimen) until the injection of hCG.

13.2 Study Results

In the two active comparative studies, results showed that on stimulation day 6/7 there were more small follicles in the CETROTIDE (cetorelix for injection) patient group than in the comparator patient groups. This was reversed on the day of hCG administration, when the number of small (11-14 mm) follicles was generally lower in the CETROTIDE (cetorelix for injection) than in the comparator groups. There was no or only a small difference with regard to the medium-size or large follicles (20 mm and over) on the day of hCG administration.

Levels of E₂ increased continuously and a pronounced increase in E₂ levels was seen the day before hCG administration in both groups [CETROTIDE (cetorelix for injection) and comparator]. On the day of hCG administration, E₂ levels were clearly higher and the increase was faster in the comparator groups than in the CETROTIDE (cetorelix for injection) group. These higher E₂ levels in the comparator groups correlate with a higher number of small follicles in this group.

The fertilization rate of CETROTIDE (cetorelix for injection) treatment versus the comparator patient groups was also similar.

Oocyte pick-up (OPU) followed by *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) as well as embryo transfer (ET) were subsequently performed. The results for CETROTIDE (cetorelix for injection) are summarized below in Table 6.

Table 6 – Results of Phase 3 Clinical Studies with CETROTIDE (cetorelix for injection) 3 mg in a single dose (sd) regimen and 0.25 mg in a multiple dose (md) regimen

Parameter	Cetrotide (cetorelix for injection) 3 mg (sd, active comparative study)	Cetrotide (cetorelix for injection) 0.25 mg (md, active comparative study)	Cetrotide (cetorelix for injection) 0.25 mg (md, non-comparative study)
No. of subjects	115	159	303
hCG administered [%]	98.3	96.2	96.0
Oocyte pick-up [%]	98.3	94.3	93.1
LH-surge [%] (LH \geq 10 U/L and P ^a \geq 1 ng/mL) ^b	0.0	1.9	1.0
Serum E ₂ [pg/ml] at day hCG ^{c,d}	1125 (470 – 2952)	1064 (341 – 2531)	1185 (311 – 3676)
Serum LH [U/L] at day hCG ^{c,d}	1.0 (0.5 – 2.5)	1.5 (0.5 – 7.6)	1.1 (0.5 – 3.5)
No. of follicles \geq 11 mm at day hCG ^e	11.2 \pm 5.5	10.8 \pm 5.2	10.4 \pm 4.5
No. of oocytes: IVF ^e	9.2 \pm 5.2	7.6 \pm 4.3	8.5 \pm 5.1
ICSI ^e	10.0 \pm 4.2	10.1 \pm 5.6	9.3 \pm 5.9
Fertilization rate: IVF ^e	0.48 \pm 0.33	0.62 \pm 0.26	0.60 \pm 0.26
ICSI ^e	0.66 \pm 0.29	0.63 \pm 0.29	0.61 \pm 0.25
No. of embryos transferred ^e	2.6 \pm 0.9	2.1 \pm 0.6	2.7 \pm 1.0
Clinical pregnancy rate [%]			
per attempt	22.6	20.8	19.8
per subject with ET	26.3	24.1	23.3

- a Progesterone
- b Following initiation of CETROTIDE (cetorelix for injection) therapy
- c Morning values
- d Median with 5th – 95th percentiles
- e Mean standard deviation

In addition to IVF and ICSI, one pregnancy was obtained after intrauterine insemination. In the five Phase 2 and Phase 3 clinical trials, 184 pregnancies have been reported out of a total of 732 patients (including 21 pregnancies following the replacement of frozen-thawed embryos).

In the 3 mg regimen, 9 patients received an additional dose of 0.25 mg of CETROTIDE (cetorelix for injection) and two other patients received two additional doses of 0.25 mg CETROTIDE (cetorelix for injection). The median number of days of CETROTIDE (cetorelix for injection) multiple dose treatment was 5 (range 1-15) in both studies.

Limited data are available in repeated administration of CETROTIDE (cetorelix for injection) in the same patient (for multiple cycles). Accordingly, it is unknown whether the efficacy remains unchanged, or whether immunogenicity and/or sensitization has been developed with the use of CETROTIDE (cetorelix for injection) in the same patient for more than one cycle.

14 NON-CLINICAL TOXICOLOGY

Cetorelix as cetorelix acetate is intended for subcutaneous injection for the control of

endogenous gonadotropin secretion in the course of a fertility program in women (daily dose: 3-10 days 0.25 mg/d, approx. 0.004 mg/kg bw). Therefore preclinical toxicity studies using parenteral administration are useful for safety evaluations and prediction of potential organ toxicity. Cetrorelix acetate was injected freshly prepared in aqueous solution, mainly as 0.3 molar mannitol solution.

A variety of organ changes - directly or indirectly related with the pharmacodynamic effects - did not show progressive properties and were morphologically and/or functionally reversible after cessation of treatment.

The described findings were qualitatively similar in rodents and non-rodents.

No direct target organ toxicity was present in acute, subacute and chronic toxicity experiments in rats and dogs. In addition, no clinical signs of drug-related local intolerance after im, iv and sc (and intraarterial and paravenous) injections were observed in rabbits and dogs. A common reaction on deposition of foreign material is a slight local inflammation and/or the accumulation of macrophages/monocytes but these reactions are of temporary nature. Cetrorelix acetate revealed no contact sensitizing properties.

No teratogenicity was detected in rats and rabbits, but early resorptions and dose-related increases of implantation losses were observed, as expected by the pharmacodynamic action of Cetrorelix. Hence, treatment during pregnancy is contraindicated. Cetrorelix had no influence on the early embryonic development and implantation (days 0-7 of pregnancy after sc injection to rats) up to the dose of 0.25 mg/day, as intended for the indication of controlled ovarian stimulation (COS) with repeated administration.

Recovery was also demonstrated from an atrophic state of reproductive organs after repeated administration to normal fertility and normal morphological structures.

Mutagenicity tests were unequivocally negative for genomutagenic and chromosomal aberration endpoints. A higher rate of polyploidy was only found in vitro at cytotoxic concentrations in one (CHL/IU) of three different cell types, showing karyotypical unstable characteristics. The result is not considered to be of any toxicological or practical relevance.

There are no objections from the toxicological point of view for the use of Cetrorelix acetate in the proposed short term and low dose treatment - daily 0.25 mg for a period of approx. 3 to 10 days - as directed.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

CETROTIDE® **Cetrorelix for injection**

Read this carefully before you start taking **CETROTIDE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CETROTIDE**.

What is CETROTIDE used for?

CETROTIDE stops your body from releasing an egg from your ovary (ovulation). It is used in assisted reproductive techniques to help you get pregnant.

How does CETROTIDE work?

CETROTIDE blocks the effect of a natural hormone, called gonadotropin-releasing hormone (GnRH). GnRH controls the secretion of another hormone, called luteinizing hormone (LH). LH is the hormone that starts ovulation (release of an egg) during your menstrual cycle. CETROTIDE controls ovulation so that it occurs at the best time for you to become pregnant.

What are the ingredients in CETROTIDE?

Medicinal ingredients: cetrorelix (as cetrorelix acetate)

Non-medicinal ingredients: mannitol

CETROTIDE comes in the following dosage forms:

Powder for solution, 0.25 mg.

Do not use CETROTIDE if you:

- are allergic to cetrorelix or mannitol, which are the ingredients in CETROTIDE
- are allergic to any component of the CETROTIDE container
- are allergic to medicines called peptide hormones
- are allergic to a hormone called gonadotropin-releasing hormone (GnRH) or to medicines called GnRH analogs
- are pregnant or think you might be pregnant
- are breastfeeding
- have moderate or severe liver problems
- have moderate or severe kidney problems

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CETROTIDE. Talk about any health conditions or problems you may have, including if you:

- are taking or have recently taken other medicines including those not requiring a prescription
- have an active allergy
- have had allergies in the past

Other warnings you should know about:

CETROTIDE will be given to you by a doctor with experience in assisted reproductive techniques.

Using CETROTIDE during more than one cycle:

Experience of using CETROTIDE during more than one cycle is limited. Your doctor will carefully look at the benefits and risks for you, if you need to use it during more than one cycle.

Ovarian Hyperstimulation Syndrome:

During or after you receive medicines that stimulate your ovaries, **ovarian hyperstimulation syndrome** can occur. With **ovarian hyperstimulation syndrome** your ovaries are enlarged and you may have abdominal bloating and pain. Although uncommon, this can be severe and life-threatening. In severe cases, hospitalization may be needed.

Birth defects and stillbirths:

Birth defects may be slightly higher in babies conceived by assisted reproductive technologies than those conceived naturally. In clinical trials where 949 women were treated with CETROTIDE, two stillbirths occurred.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Usual dose:

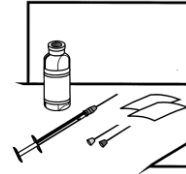
- The recommended dose of CETROTIDE is 0.25 mg once a day injected under your skin.
- It should be injected at the same time each day (every 24 hours).

How to take CETROTIDE:

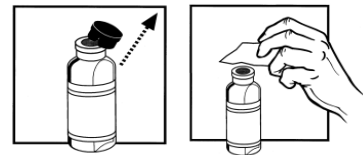
- CETROTIDE is injected under your skin in your lower abdominal area.
- Your doctor should supervise your first injection.
- You may inject CETROTIDE on your own after your first injection if your doctor has told you how to inject it and what to do if you experience an allergic reaction.
- Your doctor will tell you on what days you should take CETROTIDE.
- Always use CETROTIDE exactly as your doctor has told you to.
- Check with your doctor if you are not sure how to take it.
- You must inject CETROTIDE in a different spot in your lower abdominal area each day if you inject it more than two days in a row.
- Use CETROTIDE immediately after you have prepared it for administration.

Preparation of CETROTIDE:

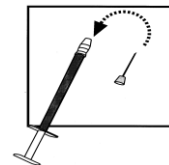
1. Clean your work surface with soap and water.
2. Wash your hands well with soap and water.
3. On a clean surface, lay out everything you need: one vial of CETROTIDE, one pre-filled syringe, one needle for mixing (yellow mark), one needle for injection (grey mark) and two alcohol wipes.



4. Flip off the plastic cover of the CETROTIDE vial. Clean the aluminum ring and rubber stopper with an alcohol wipe. Discard the alcohol wipe.



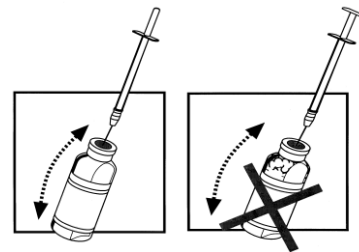
5. Take the needle for mixing (yellow mark) and remove the wrapping. Take the pre-filled syringe and remove the cover. Twist the needle onto the syringe so that it is tight. Carefully remove the cover of the needle by pulling it straight off.



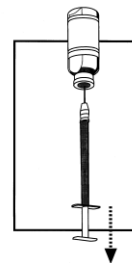
6. Push the needle through the center of the rubber stopper of the vial of CETROTIDE. Inject the water from the pre-filled syringe into the vial by slowly pushing down the plunger of the syringe. Dissolve CETROTIDE powder only with the water contained in the pre-filled syringe.



7. Without removing the needle from the vial, gently shake or rotate the vial until the solution is clear and without particles. Avoid forming bubbles. **DO NOT USE IF SOLUTION APPEARS CLOUDY, LUMPY or DISCOLOURED.**



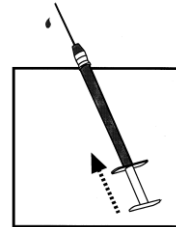
8. Draw all of the liquid in the vial into the syringe. If the liquid is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.



9. Withdraw the needle from the vial. Carefully put the cap back on the needle then twist it to detach the needle from the syringe. Discard the mixing needle into your puncture-proof container or lay it to the side. Carefully lay the syringe on a clean surface.

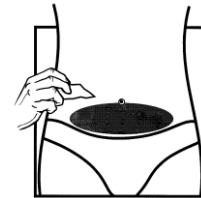
10. Take the needle for injection (grey) and remove the wrapping. Twist the needle onto the syringe so that it is tight. Carefully remove the cover of the needle by pulling it straight off.

11. Hold the syringe with the needle pointing upwards and gently flick the syringe if there are any visible air bubbles. The air bubbles will collect at the top of the syringe. If there are no air bubbles, or if there is no air space at the top of the syringe, pull the plunger back to allow for an air space of 0.1mL. Carefully replace the cap on the needle and lay the syringe down on the clean surface. Do not worry if you were unable to remove tiny air bubbles; they will do no harm. When you invert the syringe, the air space will be next to the plunger. This space will ensure that all of the medication has been injected. The air will remain in the needle. Administer the solution immediately after preparation.

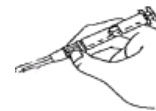


Administration of CETROTIDE:

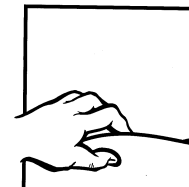
1. Choose an injection site on your lower abdominal area. It should be preferably around, but at least one inch away, from your belly button. Choose a different injection site each day to minimize local irritation. Take the second alcohol wipe, clean the skin at the injection site and allow the alcohol to dry. Keep the alcohol wipe nearby.



2. Pick up the syringe and remove the cap from the needle. Invert the syringe and hold it as if “throwing a dart”. With your other hand, gently squeeze the skin together to make a little elevation at the injection site. Using a “dart like motion”, insert the needle at a 90 degree angle (you need very little force but quick action).



3. Once the needle is inserted into the tissue all the way, inject the solution. Do this by pushing gently on the plunger with your thumb of the hand holding the syringe. Take as much time as you need to inject all the solution.



4. Immediately withdraw the needle. Clean the injection site with the clean side of the alcohol wipe using a circular motion. If there is minor oozing you may need to apply a small amount of pressure for a minute.

5. Use the syringe and needles only once. Throw away the syringe and needles immediately after use. Discard them into a disposal container or puncture-proof container with a lid that fits firmly.



Overdose:

If you think you have taken too much CETROTIDE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of CETROTIDE do not take a double dose. Discuss with your doctor when you should receive your next dose. Check with your doctor if you have any questions about this.

What are possible side effects from using CETROTIDE?

These are not all the possible side effects you may feel when taking CETROTIDE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- headache
- bruising, itching, swelling, pain or redness in your abdomen where you injected CETROTIDE
- feeling sick (nausea)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Ovarian hyperstimulation syndrome (enlarged ovaries): abdominal bloating, diarrhea, nausea, pain in the abdomen, rapid weight gain, shortness of breath, vomiting.		√	
UNCOMMON			
Allergic reactions: dizziness, fast or uneven pulse, itching (often in your groin or armpits), red itchy raised areas on your skin (hives), runny nose, serious difficulty breathing, sneezing, swelling of your tongue and throat, warm red skin, wheezing.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad

enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

CETROTIDE should be stored by the patient between 2 – 8 °C (in a refrigerator). Storage at up to 30°C for a maximum of 3 months is allowed.

Do not freeze. Store it in a cool and dry place. Protect it from excess moisture and heat. Keep the container in the outer carton in order to protect it from light.

Store the medicine out of the reach and sight of children.

Do not use CETROTIDE or the pre-filled syringe after the expiry date printed on the labels and on the carton. After the expiry date, dispose of the vial and the syringe properly.

The solution should be used immediately after preparation. Each vial and syringe should be used only once.

If you want more information about CETROTIDE:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](https://www.canada.ca/en/health-canada.html) (<https://www.canada.ca/en/health-canada.html>); <http://www.emdserono.ca>, or by calling MOMENTUM patient services program at 1-800-387-8479.

This leaflet was prepared by EMD Serono, a business of Merck KGaA, Darmstadt, Germany.

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