

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 0.25 mg cetrotide (as acetate).

After reconstitution with the solvent provided, each mL of the solution contains 0.25 mg cetrotide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Appearance of the powder: white lyophilisate

Appearance of the solvent: clear and colourless solution

The pH of the reconstituted solution is 4.0-6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature 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 gonadotropin (HMG), however, limited experience with recombinant follicle-stimulating hormone (FSH) suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide should only be prescribed by a specialist experienced in this field.

Posology

The first administration of Cetrotide 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 following injections may be self-administered 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.

The contents of 1 vial (0.25 mg cetrotide) are to be administered once daily, at 24 h intervals, either in the morning or in the evening. Following the first administration, 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.

Elderly

There is no relevant use of Cetrotide in the geriatric population.

Paediatric population

There is no relevant use of Cetrotide in the paediatric population.

Method of administration

Cetrotide is for subcutaneous injection into the lower abdominal wall.

The injection site reactions may be minimised by rotating the injection sites, delaying injection at the same site and injecting the medicinal product in a slow rate to facilitate the progressive absorption of the medicinal product.

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 gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction. The starting day of Cetrotide is depending on the ovarian response, i.e. the number and size of growing follicles and/or the amount of circulating oestradiol. The start of Cetrotide may be delayed in absence of follicular growth, although clinical experience is based on starting Cetrotide on day 5 or day 6 of stimulation.

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 gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

The starting day of Cetrotide is depending on the ovarian response, i.e. the number and size of growing follicles and/or the amount of circulating oestradiol. The start of Cetrotide may be delayed in absence of follicular growth, although clinical experience is based on starting Cetrotide on day 5 or day 6 of stimulation.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Cetrorelix is not to be used in the presence of any of the conditions listed below:

- Hypersensitivity to the active substance or any structural analogues of gonadotropin-releasing hormone (GnRH), extrinsic peptide hormones or to any of the excipients listed in section 6.1.
- During pregnancy and lactation.
- Patients with severe renal impairment.

4.4 Special warnings and precautions for use

Allergic conditions

Cases of allergic/pseudoallergic reactions, including life-threatening anaphylaxis with the first dose have been reported (see section 4.8).

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrotide is not advised in women with severe allergic conditions.

Ovarian Hyperstimulation Syndrome (OHSS)

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins

An OHSS should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

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

Repeated ovarian stimulation procedure

There is limited experience up to now with the administration of cetrorelix during a repeated ovarian stimulation procedure. Therefore, cetrorelix should be used in repeated cycles only after a careful benefit/risk 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. Limited data from clinical follow-up studies in 316 newborns of women administered cetrorelix for infertility treatments suggest that cetrorelix does not increase the risk of congenital anomalies in the offsprings.

Hepatic impairment

Cetrorelix has not been studied in patients with hepatic impairment and caution is therefore warranted.

Renal impairment

Cetrorelix has not been studied in patients with renal impairment and caution is therefore warranted. Cetrorelix is contraindicated in patients with severe renal impairment (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug-drug interaction studies have been performed with cetrorelix. *In vitro* investigations have shown that interactions are unlikely with medicinal products that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with gonadotropins or medicinal products that may induce histamine release in susceptible individuals, cannot be totally excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

Cetrorelix is not intended to be used during pregnancy and lactation (see section 4.3).

Fertility

Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the medicinal product was administered during the sensitive phase of gestation.

4.7 Effects on ability to drive and use machines

Cetrorelix has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are local injection site reactions such as erythema, swelling and pruritus that are usually transient in nature and mild in intensity. In clinical trials, these effects were observed with a frequency of 9.4% following multiple injections of Cetrorelix 0.25 mg.

Mild to moderate OHSS (WHO grade I or II) have been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Inversely, severe OHSS remains uncommon.

Uncommonly, cases of hypersensitivity reactions including pseudo-allergic/anaphylactoid reactions have been reported.

List of adverse reactions

The adverse reactions reported below are classified according to frequency of occurrence as follows: 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 OHSS (WHO grade I or II) can occur which is an intrinsic risk of the stimulation procedure (see section 4.4).

Uncommon: Severe OHSS (WHO grade III)

General disorders and administration site conditions

Common: Local reactions at the injection site (e.g. erythema, swelling and pruritus).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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 cetorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-gonadotropin-releasing hormones, ATC code: H01CC02.

Mechanism of action

Cetorelix is a luteinising hormone releasing hormone (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 gonadotropins (LH and 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.

Clinical efficacy and safety

In females, cetorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation the duration of action of cetorelix is dose dependent. At a dose of 0.25 mg 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.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of cetorelix after subcutaneous administration is about 85%.

Distribution

The volume of distribution (V_d) is $1.1 \text{ L} \times \text{kg}^{-1}$.

Elimination

The total plasma clearance and the renal clearance are $1.2 \text{ mL} \times \text{min}^{-1} \times \text{kg}^{-1}$ and $0.1 \text{ mL} \times \text{min}^{-1} \times \text{kg}^{-1}$, respectively.

The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site.

Linearity

The subcutaneous administration of single doses (0.25 mg to 3 mg cetorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetorelix. No signs of medicinal product-related local irritation or incompatibility were noted in dogs after intravenous, intraarterial and paravenous injection when cetorelix was administered in doses clearly above the intended clinical use in man.

Cetorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Mannitol

Solvent

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 2 years

After reconstitution: use immediately

6.4 Special precautions for storage

Store in a refrigerator ($2^\circ\text{C} - 8^\circ\text{C}$). Do not freeze or place next to the freezer compartment or a freezer pack.

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

The unopened medicinal product may be stored in the original package at room temperature (not above 30°C) for up to three months.

This medicinal product must be allowed to reach room temperature prior to injection. It should be removed from the refrigerator approximately 30 minutes before use.

6.5 Nature and contents of container

Powder

2 ml vials (Type I glass) with a stopper (bromobutyl rubber) and flip-off aluminium cap.

1 vial contains 0.25 mg cetorelix.

Solvent

Pre-filled syringe (Type I glass) with plunger stopper (siliconised bromobutyl rubber) and tip cap (polypropylene and styrene butadiene rubber).

1 pre-filled syringe contains 1 ml of water for injections.

Pack sizes

1 vial and 1 pre-filled syringe or 7 vials and 7 pre-filled syringes.

Additionally, for each vial the pack contains:

1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product must be allowed to reach room temperature prior to injection. It should be removed from the refrigerator approximately 30 minutes before use.

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

The reconstituted solution is without particles and clear. Do not use if the solution contains particles or if the solution is not clear.

The entire contents of the vial should be withdrawn to ensure a delivery to the patient of a dose of at least 0.23 mg cetorelix.

The solution should be used immediately after reconstitution.

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

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
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The Netherlands

8. DATE OF REVISION OF THE TEXT

Dec-2019

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.