MERCK

Cetrotide® 0,25 mg

CETRORELIX

powder and solvent for solution for injection
Active substance: Cetrorelix acetate

Name of Medicinal Product
Cetrotide 0.25 mg powder and solvent for solution for injection

Composition
One vial with 55.7 mg powder containing as active substance 0.26 - 0.27 mg cetrorelix acetate equivalent to 0,25 mg cetrorelix. Additionally, the powder contains mannitol as excipient.
One pre-filled syringe containing 1 ml water for injections.

Pharmaceutical form
Cetrotide® 0,25 mg is a powder for solution for injection.

Pharmacotherapeutic group
Cetrotide® 0,25 mg inhibits the effects of a natural hormone, called luteinising hormone releasing hormone (LHRH). LHRH regulates the secretion of another hormone, called luteinising hormone (LH), which induces ovulation during the menstrual cycle. Cetrotide® 0,25 mg inhibits premature ovulation which is undesirable during hormone treatment for ovarian stimulation as only mature egg cells are suitable for fertilisation.

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® 0,25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

Contraindications
Cetrotide is not to be used in the presence of any of the conditions listed below:
• Hypersensitivity to cetrorelix acetate, extrinsic peptide hormones or mannitol.
• During pregnancy and lactation.
• Patients with severe renal impairment.

Pregnancy and lactation
Cetrotide® 0,25 mg is not intended to be used during pregnancy and lactation (see section “Contra-indications”).

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 drug was administered during the sensitive phase of gestation.

Special warnings and precautions for use
Allergic conditions
Cases of allergic/pseudoallergic reactions, including life-threatening anaphylaxis with the first dose have been reported.

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 ovarian hyperstimulation syndrome 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 Cetrotide® 0.25 mg during a repeated ovarian stimulation procedure. Therefore, Cetrotide® 0,25 mg 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. 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

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Due to its pharmacological profile cetrorelix is unlikely to impair the patient’s ability to drive or to operate machinery.

Interaction with other medicinal products and other forms of interaction
No formal drug-drug interaction studies have been performed with Cetrotide.
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.

Posology and method of administration
Cetrotide® 0,25 mg should only be prescribed by a specialist experienced in this field.

<u>Posology</u>
The first administration of Cetrotide should be performed under the supervision of a physician and under conditions where treatment of possible pseudo-allergic reactions 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 cetrorelix) are to be administered once daily, at 24 h intervals, either in the morning or in the evening.

Following the first administration of Cetrotide® 0,25 mg, 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.

Method of administration
Cetrotide® 0,25 mg 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® 0,25 mg 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® 0,25 mg 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.

Additional information on special populations:
There is no relevant indication for the use of Cetrotide in children or geriatric populations.

Instructions for use and handling, and disposal

HOW TO MIX AND INJECT CETROTIDE
- This section tells you how to mix the powder and the sterile water (solvent) together and then how to inject your medicine.
- Before starting to use this medicine, please read these instructions the whole way through first.
- This medicine is only for you – do not let anyone else use it.
- Use each needle, vial and syringe only once.

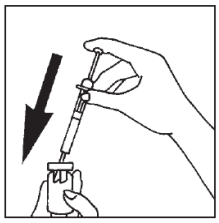
Before you start
1. This medicine must be at room temperature prior to injection. Remove from the refrigerator approximately 30 minutes before use.
2. Wash your hands
- It is important that your hands and the things you use are as clean as possible.

Lay out everything you need on a clean surface:
- one vial of powder
- one pre-filled syringe with sterile water (solvent)
- one needle with a yellow mark – for injecting the sterile water into the vial and drawing the made up medicine out from the vial
- one needle with a grey mark – for injecting the medicine into your belly
- two alcohol swabs.

Mixing the powder and water to make up your medicine
1. Remove the plastic cap from the vial
- There will be a rubber stopper underneath – keep this in the vial.
- Wipe the rubber stopper and metal ring with your first alcohol swab.

2. Adding the water from the pre-filled syringe to the powder in the vial

- Unwrap the needle with the yellow mark on it.
- Remove the cap from the pre-filled syringe and screw the yellow needle onto it. Remove the cap from the needle.
- Push the yellow needle through the centre of the rubber stopper of the vial.
- Slowly push in the plunger of the syringe to inject the water into the vial. Do not use any other sort of water.
- Leave the syringe in the rubber stopper.



3. Mixing the powder and water in the vial

- While carefully holding the syringe and vial, swirl gently to mix the powder and water together. When it is mixed, it will look clear and have no particles in it.
- Do not shake or you will create bubbles in your medicine.

4. Re-filling the syringe with the medicine from the vial

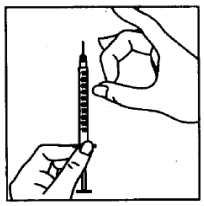
- Turn the vial upside down.
  Then, gently pull back the plunger, in order to draw the medicine from the vial into the syringe. Take care not to pull out completely the plunger with the attached plunger stopper. In case you pulled out the plunger with the plunger stopper by mistake, make sure to discard the dose as sterility will be lost, and prepare a new dose (and restart from step 1).
- If any medicine is left in the vial, pull out the yellow needle until the end of the needle is just inside the rubber stopper. If you look from the side through the gap in the rubber stopper, you can control the movement of the needle and the liquid.
- Make sure that you collect all of your medicine from the vial.

- Put the cap back on the yellow needle. Unscrew the yellow needle from the syringe and lay down the syringe.

Preparing the injection site and injecting your medicine

1. Removing air bubbles

- Unwrap the needle with the **grey** mark on it. Screw the grey needle onto the syringe and remove the cap from the grey needle.
- Hold the syringe with the grey needle pointing upwards and check for any air bubbles.
- To remove air bubbles, gently flick the syringe until all the air collects at the top – then slowly push the plunger in until the air bubbles are gone.
- Do not touch the grey needle and do not let the needle touch any surface.

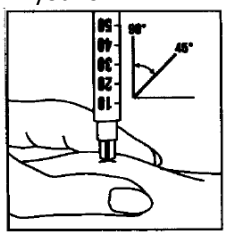


2. Clean the injection site

- Choose an injection site on your belly. It is best around the belly button (navel). To reduce skin irritation, select a different part of your belly each day.

- Clean the skin at your chosen injection site with your second alcohol swab - use a circular motion.

3. Piercing your skin
- Hold the syringe in one hand – like you would hold a pencil.
- Gently pinch up the skin around where you are going to inject and hold this firmly with your other hand.
- Slowly push the grey needle completely into your skin at an angle of about 45 to 90 degrees – then let go of your skin.



4. Injecting your medicine
- Gently pull back the plunger of the syringe. If blood appears, follow Step 5 below.
- If no blood appears, **slowly** push the plunger in to inject your medicine.
- When the syringe is empty, take out the grey needle slowly at the same angle.
- Use your second alcohol swab to gently apply pressure where you have just injected.

5. If blood appears:
- take out the grey needle slowly at the same angle
- use your second alcohol swab to gently apply pressure where you have just pierced your skin
- empty your medicine into a sink and follow Step 6 below
- wash your hands and start again with a new vial and pre-filled syringe.

6. Disposal
- Use each needle, vial and syringe only once.
- Put the cap back on the needles so that they are safe to be thrown away.
- Ask your pharmacist how to safely dispose of used needles, vial and syringe.

Overdose
Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects. Therefore, in case of overdosage no specific measures are required.
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.

Missing a dose
If you missed to administer Cetrotide® 0,25 mg on one day, please contact your doctor immediately and ask for advice.
Ideally Cetrotide® 0,25 mg should be administered at 24 hours intervals. But if you missed to administer Cetrotide® 0,25 mg at the right time it is no problem to administer this dose at a different time of the same day.

Undesirable effects
Mild and transient reactions at the injection site, e.g. erythema, itching, and swelling.
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. Uncommonly, cases of hypersensitivity reactions including pseudo-allergic/anaphylactoid reactions have been reported.

Mild to moderate ovarian hyperstimulation syndrome (OHSS) (WHO grade I or II) have been commonly reported which is an intrinsic risk of the stimulation procedure (see section “Special warnings and precautions for use”). Inversely, severe OHSS remains uncommon.

Symptoms like abdominal pain, tension, nausea, vomiting, diarrhoea and breathing difficulties may indicate an OHSS. Please inform your doctor immediately, if you feel such symptoms.
If you notice any unwanted effect not mentioned in this leaflet or if you are unsure about the effect of this medicine, please inform your doctor or pharmacist.

The adverse reactions reported below are classified according to frequency of occurrence as follows:

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

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 (see "Special warnings and precautions for use")
	Uncommon	Severe ovarian hyperstimulation syndrome (WHO grade III)
General disorders and administration site conditions	Common	Local reactions at the injection site (e.g. erythema, swelling and pruritus) have been reported. Usually they were transient in nature and of mild intensity. The frequency as reported in clinical trials was 9.4% following multiple injections of 0,25 mg cetrorelix.

Incompatibilities
As cetrorelix is incompatible with several substances of common parenteral solutions it should be dissolved only by using water for injections.

Pharmacological properties
Pharmacodynamic properties
Pharmacotherapeutic group: LHRH-Antagonist, ATC code: G03X.
Cetrorelix is a luteinising hormone releasing hormone (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 gonadotropins (LH and 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 0,25 mg per injection repeated injections every 24 hours 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.

Pharmacokinetic properties
The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.
The total plasma clearance and the renal clearance are 1.2 ml x min^{-1} x kg^{-1} and 0.1 ml x min^{-1} x kg^{-1}, respectively. The volume of distribution (Vd,area) is 1.1 l x kg^{-1}. 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. The subcutaneous administration of single doses (0,25 mg to 3 mg cetrorelix) and also daily dosing over 14 days show linear kinetics.

Nature and content of container
Packs with 1 or 7 Type I glass vials each containing 55.7 mg powder for solution for injection sealed with a rubber stopper.
Additionally, for each vial the packs contain
• one pre-filled syringe with solvent (water for injections) for parenteral use for dissolving the powder in the vial
• one injection needle with a yellow mark for injecting the water into the vial and withdrawing the solution from the vial
• one injection needle with a grey mark for injecting the solution
• two alcohol swabs for cleaning purposes.

Storage and stability note
The Cetrotide® 0,25 mg powder in the vial and the solvent in the pre-filled syringe have the same expiry date. It is printed on the labels and on the carton. Do not use the Cetrotide® 0,25 mg powder or the solvent after this date.
The solution should be used immediately after preparation.
Store at 2- 8 °C. Keep the container in the outer carton in order to protect it from light.
Store drugs out of children's reach!

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