Prescribing Information

Cetrotide® 0.25

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 cetrorelix (as acetate).
After reconstitution with the solvent provided, each ml of the solution contains 0.25 mg cetrorelix.

For a 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 follicule-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 cetrorelix) 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.

Older people
There is no relevan indication for the use of Cetrotide in geriatric population.

Paediatric population
There is no relevsnt use if 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 product in a slow rate to facilitate the progressive absorption of the 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.

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.

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

4.3 Contraindications

- 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.
- Pregnancy and lactation.
- Postmenopausal women.
- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and precautions for use

Allergic conditions
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 during a repeated ovarian stimulation procedure. Therefore Cetrotide should be used in repeated cycles only after a careful risk/benefit evaluation.

4.5 Interaction with other medicinal products and other forms of interaction

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, although there has been no evidence of drug-interactions, especially with commonly used medicinal products, gonadotropins or products that may induce histamine release in susceptible individuals, the possibility of an interaction cannot be totally excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
Cetrotide 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

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

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported side effects 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 Cetrotide 0.25 mg.

Mild to moderate ovarian hyperstimulation syndrome (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 (≥ 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 (see section 4.4).
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

Reporting of suspected adverse reaction

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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.

Clinical efficacy and safety

In females, cetrorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. 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.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

The volume of distribution (V_d) is 1.1 l x kg^{-1}

Elimination
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 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 cetrorelix) 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 cetrorelix. No signs of medicinal product-related local irritation or incompatibility were noted in dogs after intravenous, intra-arterial and paravenous injection when cetrorelix was administered in doses clearly above the intended clinical use in man.

Cetrorelix 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

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C.
Keep the vial(s) in the outer carton in order to protect from light.

6.5 Nature and contents of container

Packs with 1 or 7 Type I glass vials sealed with a rubber stopper.

Additionally for each vial the packs contain:

1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 1 ml solvent for parenteral use

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

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.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 0.23 mg cetrorelix.

The solution should be used immediately after reconstitution.

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

7. REGISTRATION NO.

117 19 29780 00, 117 19 29780 01

8. MANUFACTURER

Merck KGaA, Darmstadt, Germany

9. REGISTRATION HOLDER

Merck Serono Ltd., 18 Hakishon St., Yavne

10. DATE OF REVISION OF THE TEXT

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in June 2016