CETROTIDE

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

CETROTIDE 0,25 mg **Injection**

CETROTIDE 0,25 mg SOLVENT **Injection**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cetrotide 0,25 mg contains 0,26 – 0,27 mg cetrorelix acetate equivalent to 0,25 mg cetrorelix.

Cetrotide 0,25 mg Solvent contains 1 ml Water for Injections.

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 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 medical specialist and under conditions where treatment of possible 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. Facilities for the treatment of such reactions should be immediately available.

Elderly

There is no relevant use of Cetrotide in the elderly 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.

Administration in the morning: Treatment with Cetrotide should commence on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after the 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 estradiol. 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 the 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 estradiol. 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.

4.3 Contraindications

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

- Hypersensitivity to cetrorelix acetate, 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/pseudo-allergic 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 (OHSS) can occur. However, this event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome (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 Cetrotide during a repeated ovarian stimulation procedure. Therefore, Cetrotide should be used in repeated cycles only after a careful risk/benefit evaluation.

Congenital anomalies

The prevalence of congenital anomalies after the use of assisted reproductive technologies (ART) with or without GnRH antagonists may be slightly higher than after spontaneous conceptions although it is unclear whether this is related to factors inherent to the couple's infertility or the ART procedures.

Limited data from clinical follow-up studies in 316 newborns of women administered Cetrotide for infertility treatments suggest that Cetrotide does not increase the risk of congenital anomalies in the offsprings.

Hepatic impairment

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

Renal impairment

Cetrotide has not been studied in patients with renal impairment and caution is therefore warranted. Cetrotide is contraindicated in patients with severe renal impairment.

4.5 Interaction with other medicines 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 medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with gonadotropins or products that may induce histamine release in susceptible individuals, cannot be entirely excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

Cetrotide is not intended to be used during pregnancy and lactation.

Fertility

Studies in animals have indicated that Cetrotide 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 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 Cetrotide 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 events reported below are classified according to the frequency of occurrence as follows:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1000 to < 1/100
Rare	≥ 1/10000 to < 1/1000
Very rare	< 1/10000

Immune system disorders

Uncommon: Systemic allergic/pseudo-allergic reactions including life-threatening anaphylaxis (see section 4.4)

Nervous system disorders

Uncommon: Headache

Gastrointestinal disorders

Uncommon: Nausea

Reproductive system and breast disorders

Common: Mild to moderate 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.

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

21.12 Hormone inhibitors

Pharmacotherapeutic Group: LHRH-Antagonist

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, intraarterial 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

As Cetrotide is incompatible with several substances of common parenteral solutions it should only be dissolved using the solvent provided or Water for Injections

6.3 Shelf life

Unopened vial: 2 years

After reconstitution: use immediately

6.4 Special precautions for storage

- Store between 2 °C – 8 °C in a refrigerator. Do not freeze.

- Keep the container in the original carton in order to protect from light.
- Within its shelf-life, the patient may remove the product from the refrigerator, and it may be stored at or below 30 °C for one single period of up to a maximum of 3 months.
- The product must not be used after expiry date.
- The solution should be used immediately after reconstitution and not stored.

6.5 Nature and contents of container

Cetrotide 0,25 mg	A white lyophilised cake in a colourless glass vial with a grey rubber stopper, aluminium cap and blue plastic flip-off cap.
Cetrotide 0,25 mg Solvent	A clear, colourless solution in a pre-filled glass syringe without a needle.

Pack 1:

Cetrotide 0,25 mg	1 glass vial containing a lyophilised cake. 1 pre-filled syringe, with 1ml solvent for reconstitution of Cetrotide 0,25 mg. 1 injection needle (20 gauge). 1 hypodermic injection needle (27 gauge). 2 alcohol swabs.

Pack 2

Cetrotide 0,25 mg	7 glass vials containing lyophilised cakes. 7 pre-filled syringes, each with 1ml solvent for reconstitution of Cetrotide 0,25 mg. 7 injection needles (20 gauge). 7 hypodermic injection needles (27 gauge). 14 alcohol swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

- Cetrotide 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 cetrorelix.
- The solution should be used immediately after reconstitution.

Any unused (including expired) product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Merck (Pty) Ltd

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Longmeadow Business Estate South,

Modderfontein, 1645

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NAME AND ADDRESS OF MANUFACTURER:

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8. REGISTRATION NUMBERS

CETROTIDE 0,25mg A39/21.12/0064

CETROTIDE 0,25 mg SOLVENT A40/34/0162

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

CETROTIDE 0,25mg 18/04/2008

CETROTIDE 0,25 mg SOLVENT 03/11/2007

10. DATE OF REVISION OF THE TEXT

17/01/2022