For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Cetrorelix 0.25mg Powder and Solvent for Solution for Injection

Asporelix

0.25mg Powder

For Subcutaneous / Single Use Injection

COMPOSITION :
Each vial contains:
Cetrorelix (as acetate).....0.25 mg
(Lyophilized) Excipients: Mannitol BP
Excipients: Mannitol B.P

Each vial of **Asporelix** is accompanied by an ampoule of Sterile Water for Injection 1mL.

Description:
Asporelix 0.25 (Cetrorelix 0.25mg Powder): Awhite to off white lyophilized cake or powder Sterile Water for Injection 1mL (Diluent): A clear colourless liquid, odourless.
After reconstitution: The solid dissolves completely, leaving no visible residue as un-dissolved matter. The constituted solution should not significantly less clear than equal volume of water for injection contained in a similar vessel and examined similarly. The pH of reconstituted solution is between 4.0 to 6.0

PHARMACOLOGICAL PROPERTIES:

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.

The antagonistic hormonal effects of cetrorelix is fully reversible after termination of treatment.

Pharmacokinetic Properties:
Absorption
The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.

Distribution
The volume of distribution (Vd) 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

INDICATIONS :
Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques. Cetrorelix 0.25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle-stimulating hormone (FSH) suggested similar efficacy.

DOSAGE AND ADMINISTRATION:
Asporelix 0.25 should only be prescribed by a specialist experienced in this field.

Dosage
Asporelix 0.25 is not intended to be self-administered. This product is intended to be administered by healthcare professionals who are familiar with reconstitution techniques only. Administration of Asporelix
0.25 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 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 cetrorelix in the geriatric population.
Paediatric population
There is no relevant use of cetrorelix in the paediatric population.

Method of Administration
Asporelix 0.25 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 Asporelix 0.25 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 Asporelix 0.25 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 Asporelix 0.25 may be delayed in absence of follicular growth, although clinical experience is based on starting Asporelix 0.25 on day 5 or day 6 of stimulation.

Administration in the evening:
Treatment with Asporelix 0.25 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 Asporelix 0.25 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 Asporelix
0.25 may be delayed in absence of follicular growth, although clinical experience is based on starting

Asporelix 0.25 on day 5 or day 6 of stimulation.

Instructions for Use

This product is not intended to be self-administered. This product is intended to be administered by healthcare professionals who are familiar with reconstitution techniques only. This medicine must be allowed to reach room temperature prior to injection. It should be removed from the refrigerator approximately 30 minutes before use.

The diluent for reconstitution (1 mL sterile water for injection) is provided together with the powder.
A ready-to-use solution is prepared by injecting 1 mL of the sterile water for injection (provided with pack) into the vial containing the dry powder. On reconstitution, the solid dissolves completely, leaving no visible residue as un-dissolved matter and should not be significantly less clear than an equal volume of the sterile water for injection in a similar vessel. The pH of reconstituted solution is between 4.0 to 6.0. 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. Asporelix 0.25 powder must only be reconstituted with the sterile water for injection contained in the ampoule provided together in the box. Use the reconstituted solution immediately, do not store solution for later use. The contents of the vial is for single use only, any unused solution must be discarded in accordance with local requirements.

Asporelix 0.25 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.
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. Asporelix 0.25 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 medicinal product or waste material should be disposed of in accordance with local requirements.

Special precautions for disposal and other handling

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Contraindications:

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

Warnings and Precautions:

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 Asporelix 0.25 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 316newborns of women administered cetrorelix for infertility treatments suggest that cetrorelix does not increase the risk of congenital anomalies in the off springs.

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.

Interactions with other Medicines:
No formal drug-drug interaction studies have been performed with cetrorelix. 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.

Fertility, pregnancy and lactation:

Pregnancy and breastfeeding
Asporelix 0.25 is not intended to be used during pregnancy and lactation.

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

Effects on ability to drive and use machines:
Asporelix 0.25 has no or negligible influence on the ability to drive and use machines.

Side 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. 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

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.

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)

Symptoms and Treatment of Overdose:

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

Non-specific toxic symptoms were observed in rodents after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

Storage Condition:

Store unopened vial and diluent in refrigerator between 2°C to 8°C. Do not freeze. Store in the original package. Protect from light.

Reconstituted solution: Use immediately after reconstitution. The contents of the vial is for single use only, any unused solution must be discarded in accordance with local requirements.

Incompatibilities:

This medicinal product must not be mixed with other medicinal products except those mentioned in Special precautions for disposal and other handling.

Shelf Life:

Asporelix 0.25: 24 months

Sterile Water for Injection (Diluent): 36 month

Presentation:
Pack size: 1 vial of lyophilized powder with 1 ampoule of sterile water for injection (diluent)

Vial description: USP Type 1 tubular, concaved bottom glass vial of 2ml size/ capacity with 13 mm slotted rubber bung and 13 mm aluminium flip off seal with transparent blood red coloured polypropylene flip off disc.

Ampoule description (diluent): 1 ml volume, clear colourless borosilicate USP Type 1 glass with concave bottom and blue band at neck.

Leaflet Revision Date: May 2022

Manufacturer

Bharat Serums and Vaccines Limited
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