Instructions for administration:
1. **Asporelix**™ (Cetrorelix Acetate for Injection) should only be reconstituted with the diluent provided (Sterile Water for Injection I.P.) with the pack.
2. Aseptically withdraw the entire contents of the diluent ampoule into a syringe. Push the needle through the center of the rubber stopper of the appropriate **Asporelix**™ (Cetrorelix Acetate for Injection) vial and slowly inject the diluent into the vial.
3. Leaving the syringe in the vial, gently swirl the vial until the solution is clear and without residues. Vigorous shaking with bubble formation should be avoided.
4. Draw the total contents of the vial into the syringe. If necessary, invert the vial and pull back the needle as far as needed to withdraw the entire contents at the vial. This ensures a delivery in the patient of a dose of at least 0.23 mg cetrorelix.
5. Do not use if the solution contains particles or if the solution is not clear.
6. The solution should be used immediately after reconstitution.
7. The Site of injection- preferably abdomen should be varied dally when being used in the multiple dose regimen.

Hepatic impairment: The use of **Asporelix**™ (Cetrorelix Acetate for Injection) is contraindicated in moderate to severe hepatic impairment.
Renal impairment: Use of **Asporelix**™ (Cetrorelix Acetate for Injection) is contraindicated in moderate to severe renal impairment.

Incompatibilities:
As cetrorelix is incompatible with several substances of common parenteral solutions, it should be dissolved only by using the supplied Sterile Water for Injection.

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

Storage & Handling:
Store between 2°C to 8°C. Do not freeze. Protect from light.
Keep out of reach of children.

Shelf Life:
Unopened vial: 2 years.
Do not use after expiry date.
Reconstituted product: Use immediately after reconstitution.

Presentation:
Vial containing 0.25 mg Lyophilized powder for Injection of Cetrorelix Acetate, along with ampoule containing 1ml of Sterile Water for Injection I.P. as diluent.

To report Suspected Adverse Reactions, contact Bharat Serums and Vaccines at pv@bharatserums.com or visit the website www.bharatserums.com/adverse.html

Manufactured in India by:
BHARAT SERUMS AND VACCINES LIMITED
Plot No. K-27, Additional M.I.D.C., Ambernath (E) - 421 501.

IN90305D0

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

℞ Cetrorelix Acetate for Injection 0.25 mg

अॅस्पोरेलिक्स
Asporelix®
0.25 mg

(Lyophilized)
For Subcutaneous use only
For Single use only

Dosage Form:
Lyophilized Powder for Injection.

Composition:
Each Vial Contains:
Cetrorelix (as acetate) ..... 0.25 mg
(Lyophilized)
Excipients: Mannitol I.P.

Description:
Asporelix™ (Cetrorelix Acetate for Injection) is a sterile Lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection I.P.

Clinical Pharmacology:
Cetrorelix Acetate for Injection is a synthetic decapeptide with gonadotropin releasing hormone (GnRH) antagonistic activity.

Mechanism of Action:
GnRH induces the production and release of luteinizing hormone (LH) and follicle stimulatlng hormone (FSH) from the gonadotrophic cells of the anterior pituitary. Due to a positive estradiol (E2) feedback at midcycle, GnRH liberation is enhanced resulting in an LH surge. This LH surge induces the ovulation of the dominant follicle, resumption of oocyte meiosis and subsequently luteinization as indicated by rising progesterone levels.
Cetrorelix competes with natural GnRH for binding to membrane receptors on pituitary cells and thus controls the release of LH and FSH in a dose dependent manner. The onset of LH suppression is approximately one hour with the 3 mg dose and two hours with the 0.25 mg dose. This suppression is maintained by continuous treatment and there is a more pronounced effect on LH than on FSH. An initial release of endogenous gonadotropins has not been detected with cetrorelix, which is consistent with an antagonist effect. The effects of cetrorelix on LH and FSH are reversible after discontinuation of treatment. In women, celrorelix delays the LH surge, and consequently ovulation, in a dose dependent fashion. FSH levels are not affected at the doses used during controlled ovarian stimulation. Following a single 3 mg dose of cetrorelix duration of action of at least 4 days has been established. A dose of cetrorelix 0.25 mg every 24 hours has been shown to maintain the effect.

Pharmacokinetics:
The pharmacokinetic parameters from literature studies of single and multiple doses of Cetrorelix Acetate for Injection in adult healthy female subjects are summarized in the following table:

Pharmacokinetic parameters of Cetrorelix for Injection following 3 mg single or 0.25 mg single and multiple (daily for 14 days) subcutaneous (SC) administration

	Single dose 3 mg	Single dose 0.25 mg	Multiple dose 0.25 mg
No. of subjects	**12**	**12**	**12**
tmax* (h)	1.5 (0.5 – 2)	1.0 (0.5 – 1.5)	1.0 (0.5 – 2)
t ½* (h)	62.8 (38.2 – 108)	5.0 (2.4 – 48.8)	20.6 (4.1 – 179.3)
C max (ng / ml)	28.5 (22.5 – 36.2)	4.97 (4.17 – 5.92)	6.42 (5.18 – 7.96)
AUC (ng.h/ml)	536 (451 – 636)	31.4 (23.4 – 42.0)	44.5 (36.7 – 54.2)
** CL (ml/min.kg)	1.28a		
Vz (l/kg)	1.16a		

* median (min-max),
** arithmetic mean,
T_{max} -Time to reach observed maximum plasma concentration.
$t^1/_2$ - Elimination half-life,
C_{max} -Maximum plasma concentration; multiple dose $C_{ss, max}$,
AUC -Area under the Curve; single dose AUC_{0-inf} multiple dose AUCt,
CL-Total plasma clearance,
Vz-Volume of distribution,
a - Based on IV administration.

Size: 200 x 200 mm

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Cetrorelix is rapidly absorbed following subcutaneous injection with maximal plasma concentrations being achieved approximately one to two hours after administration. The mean absolute bioavailability of cetrorelix following subcutaneous administration to healthy female subjects is 85%.

The volume of distribution of cetrorelix following a single intravenous dose of 3 mg is about 1 l/kg. *In vitro* protein binding to human plasma is 86%. Cetrorelix concentrations in follicular fluid and plasma were similar on the day of oocyte pick-up in patients undergoing controlled ovarian stimulation. Following subcutaneous administration of cetrorelix 0.25 mg plasma concentrations of cetrorelix were below or in the range of the lower limit of quantitation on the day of oocyte pick-up and embryo transfer.

After subcutaneous administration of 10mg cetrorelix to females and males, cetrorelix and small amounts of (1-9), (1-7), (1-6), and (1-4) peptides were found in bile samples over 24 hours. In *in-vitro* studies, cetrorelix was stable against phase I- and phase II-metabolism. Cetrorelix was transformed by peptidases, and the (1-4) peptide was the predominant metabolite.

Following subcutaneous administration of 10mg cetrorelix males and females, only unchanged cetrorelix was detected in urine. In 24 hours, cetrorelix and small amounts of the (1-9), (1-7), (1-6), and (1-4) peptides were found in bile samples. 2-4% of the dose was eliminated in the urine as unchanged cetrorelix, while 5-10% was eliminated as cetrorelix and the four metabolites in bile. Therefore, only 7-14% of the total dose was recovered as unchanged cetrorelix and metabolites in urine and bile up to 24 hours. The remaining portion of the dose may not have been recovered since bile and urine were not collected for a longer period of time.

Pharmacokinetic Investigations have not been performed either in subjects with impaired renal or liver function, or in the elderly, or in children. There is no evidence of differences in pharmacokinetic parameters for cetrorelix between healthy subjects and patients undergoing controlled ovarian stimulation.

Indications:
Cetrorelix is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.

Contra-indications:
- Hypersensitivity to cetrorelix acetate, extrinsic peptide hormones or mannitol.
- Known hypersensitivity to GnRH or any other GnRH analogs.
- Known or suspected pregnancy and lactation.
- Patients with moderate and severe renal or hepatic impairment.
- Post menopausal women.

Warnings and Precautions:
Asporelix™ (Cetrorelix Acetate for Injection) should be prescribed by specialists who are experienced in fertility treatment. Before starting treatment with cetrorelix, pregnancy must be excluded. Cetrorelix should not be prescribed if a patient is pregnant.

Caution is advised in patients with hypersensitivity to GnRH. These patients should be carefully monitored after the first Injection. A severe anaphylactic reaction associated with cough, rash, and hypotension, was observed in one patient after seven months of treatment with cetrorelix (10mg/day) in a study as reported for an indication unrelated to infertility. Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition.

Treatment with cetrorelix is not advised in women with severe allergic conditions.

During or following ovarian stimulation an ovarian hyperstimulatlon 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 centres practice. 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 risk / benefit evaluation.

Prior to therapy with cetrorelix acetate for injection, patients should be informed of the duration of treatment and monitoring procedures that will be required. The risk of possible adverse reactions should be discussed.

From literature studies, after the exclusion of preexisting conditions, enzyme elevations (ALT, AST, GGT, alkaline phosphatase) were found in 1-2% of patients receiving cetrorellx during controlled ovarian stimulation. The elevations ranged up to three times the upper limit of normal. The clinical significance of these findings was not determined. During stimulation with human menopausal gonadotropin, cetrorelix had no notable effects on hormone levels aside from inhibition of LH surges.

Pregnancy & Lactation:
The use of **Asporelix™** (Cetrorelix Acetate for Injection) is contraindicated in pregnant women.

The fetal resorption observed in animal studies is a logical consequence of the alteration in hormonal levels resulting from the antigonadotrophic properties of cetrorelix which could result in fetal loss in humans as well. Therefore, this drug should not administered to pregnant women.

It Is not known whether cetrorelix is excreted In human milk. Because many drugs are excreted in human milk, and because the effects of cetrorelix on lactation and/or the breast-fed child have not been determined, the use of **Asporelix™** (Cetrorelix Acetate for Injection) is not recommended in nursing mothers.

Drug Interactions:
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, interactions with gonadotropins or medicinal products including drugs that may induce histamine release in susceptible individuals, may occur.

Side effects:
Local reactions at the injection site (e.g., erythema, redness, itching, bruising, swelling and pruritus) have been reported. Usually they were transient in nature and mild intensity. Rare cases of hypersensitivity reactions including pseudo-allergic / anaphylactoid reactions have also been reported. Nausea and headache have also been reported.

Mild to moderate ovarian hyperstimulation syndrome (WHO grade I or II) can occur which is an intrinsic risk of the stimulation procedure. Uncommonly severe ovarian hyperstimulation syndrome (WHO grade III) can occur.

Two still births were reported in phase 3 studies from literature with cetrorelix acetate for Injection. As reported in the literature study, in clinical follow up studies of 316 newborns of women administered cetrorelix were reviewed. One infant of a set of twin neonates was found to have anencephaly at birth and died after four days. The other twin was normal. Developmental findings from ongoing baby follow up included a child with a ventricular septal detect and another child with bilateral congenital glaucoma.

Four pregnancies that resulted in therapeutic abortion in Phase 2 and Phase 3 controlled ovarian stimulation reported in the literature had major anomalies (diaphragmatic hernia, trisomy 21, Klinefelter syndrome, polymalformation, and trisomy 18). In three of these four cases, intracytoplasmic sperm Injection (ICSI) was the fertilization method employed; in the fourth case, *In vitro* fertilization (IVF) was the method employed.

The minor congenital anomalies reported include: supernumerary nipple, bilateral strabismus, imperforate hymen, congenital nevi, hemangiomata, and QT syndrome. The causal relationship between the reported abnormalities and cetrorelix is unknown. Multiple factors, genetic and others (including, but not limited to ICSI, IVF, gonadotropins, and progesterone) make causal attribution difficult to study.

Overdosage:
Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects. There have been no reports of overdosage with cetrorelix injection in humans. Single doses up to 120 mg cetrorelix has been well tolerated in patients treated for other indications without signs of overdosage.

As reported in the literature, 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.

Dosage and Administration:
Asporelix™ (Cetrorelix Acetate for Injection) should only be prescribed by a specialist experienced in this field. **Asporelix™** (Cetrorelix Acetate for Injection) is for subcutaneous injection into the lower abdominal wall.

Ovarian stimulation therapy with gonadotropins (FSH, hMG) is started on cycle Day 2 or 3. The dose of gonadotropins should be adjusted according to individual response. **Asporelix™** (Cetrorelix Acetate for Injection) should be administered subcutaneously once daily during' the early - to mid-follicular phase.

Asporelix™ (Cetrorelix Acetate for Injection) is administered on either stimulation day 5 (morning or evening) or day 6 (morning) and continued daily until the day of hCG administration.

When assessment by ultrasound shows a sufficient number of follicles of adequate size, hCG is administered to induce ovulation and final maturation of the oocytes. No hCG should be administered if the ovaries show an excessive response to the treatment with gonadotropins to reduce the chance of developing ovarian hyperstimulation syndrome (OHSS).

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