



MEMPHIS VISION CARE PVT LTD
CETRORELIX ACETATE INJECTION 0.25 MG/0.5 ML
(IETROCARE)

1.3 Product Information

1. Name of the drug product

Cetorelix acetate Injection 0.25mg/0.5ml (IETROCARE)

2. Qualitative and quantitative composition

Each 0.5 ml PFS contains

Cetorelix acetate0.25 mg

Water for injection.....Q.S.

3. Pharmaceutical form

Solution for injection in pre-filled syringes.

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 Cetorelix was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle-stimulating hormone (FSH) suggested similar efficacy.

4.2 Posology/Dosage and method of administration

Cetorelix should only be prescribed by a specialist experienced in this field.

Posology

The first administration of Cetorelix 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 cetorelix) 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.

Elderly

There is no relevant use of Cetorelix in the geriatric population.

Paediatric population

There is no relevant use of Cetorelix in the paediatric population.

Method of administration

Cetorelix is for subcutaneous injection into the lower abdominal wall.



MEMPHIS VISION CARE PVT LTD
CETRORELIX ACETATE INJECTION 0.25 MG/0.5 ML
(IETROCARE)

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

Administration in the evening

Treatment with Cetorelix 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 Cetorelix 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 Cetorelix may be delayed in absence of follicular growth, although clinical experience is based on starting Cetorelix on day 5 or day 6 of stimulation.

4.3 Contraindications

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

- 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.
- During pregnancy and lactation.
- Patients with severe renal impairment.

4.4 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 Cetorelix 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.



MEMPHIS VISION CARE PVT LTD
CETRORELIX ACETATE INJECTION 0.25 MG/0.5 ML
(IETROCARE)

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 cetorelix during a repeated ovarian stimulation procedure. Therefore, cetorelix 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 316 newborns of women administered cetorelix for infertility treatments suggest that cetorelix does not increase the risk of congenital anomalies in the offsprings.

Hepatic impairment

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

Renal impairment

Cetorelix has not been studied in patients with renal impairment and caution is therefore warranted.

Cetorelix is contraindicated in patients with severe renal impairment (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug-drug interaction studies have been performed with cetorelix. *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.

4.6 Fertility, pregnancy and lactation

Pregnancy & Breastfeeding

Ietrocare is not intended to be used during pregnancy and lactation (see section 4.3).

Fertility

Studies in animals have indicated that cetorelix 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

Ietrocare 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



MEMPHIS VISION CARE PVT LTD
CETRORELIX ACETATE INJECTION 0.25 MG/0.5 ML
(IETROCARE)

clinical trials, these effects were observed with a frequency of 9.4% following multiple injections of Ietrocare 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 reactions reported below are classified according to frequency of occurrence as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

<i>Immune system disorders</i>	
Uncommon:	Systemic allergic/pseudo-allergic reactions including life-threatening anaphylaxis.
<i>Nervous system disorders</i>	
Uncommon:	Headache
<i>Gastrointestinal disorders</i>	
Uncommon:	Nausea
<i>Reproductive system and breast disorders</i>	
Common:	Mild to moderate OHSS (WHO grade I or II) can occur which is an intrinsic risk of the stimulation procedure (see section 4.4).
Uncommon:	Severe OHSS (WHO grade III)
<i>General disorders and administration site conditions</i>	
Common:	Local reactions at the injection site (e.g. erythema, swelling and pruritus).

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 cetorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration

5. Pharmacological properties

5.1 Pharmacodynamics properties

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

Mechanism of action



MEMPHIS VISION CARE PVT LTD
CETRORELIX ACETATE INJECTION 0.25 MG/0.5 ML
(IETROCARE)

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 $1.1 \text{ L} \times \text{kg}^{-1}$.

Elimination

The total plasma clearance and the renal clearance are $1.2 \text{ mL} \times \text{min}^{-1} \times \text{kg}^{-1}$ and $0.1 \text{ mL} \times \text{min}^{-1} \times \text{kg}^{-1}$, 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



MEMPHIS VISION CARE PVT LTD
CETRORELIX ACETATE INJECTION 0.25 MG/0.5 ML
(IETROCARE)

6.1 List of excipients

Mannitol, Glacial acetic acid

Solvent

Water for Injection

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

24 months

6.4 Special precautions for storage

Store between 2°C-8°C.

Keep out of reach of children.

6.5 Nature and contents of container

1 ml clear PFS with Needle (USP Type-I) with Nested Bung and Berral.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None

7. Manufactured By

Memphis Vision Care Pvt Ltd
WHO-GMP Certified Company
Plot No: 450, Opposite Nirma Factory
Besides Jay Banas metals Pvt Ltd
Chhatral, Tal. Kalol, Dist: Gandhinagar

8. Marketed in Nigeria by

Ignite Pharma Nigeria Limited
30, Ajegunle Village, Magboro,
Ogun State, Nigeria

Exported By

Alvita Pharma Pvt Ltd.
B-203, Gopal Palace,
Nr. Nehru Nagar
Satelite Road, Ambavadi,
Ahmedabad-380015, India

9. NAFDAC REGISTRATION NUMBER(S)