# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Ceziboe 0.25 mg solution for injection in pre-filled syringe

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 1 ml solution contains 0.25 mg cetrorelix (as acetate).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear, colourless solution free from visible particles with a pH from 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 cetrorelix was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle-stimulating hormone (FSH) suggested similar efficacy.

### 4.2 Posology and method of administration

Cetrorelix should only be prescribed by a specialist experienced in this field

Posology

The first administration of cetrorelix 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 syringe (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.

*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

Cetrorelix 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 medicinal product.

*Administration in the morning:* Treatment with cetrorelix 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 cetrorelix 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 cetrorelix may be delayed in absence of follicular growth, although clinical experience is based on starting cetrorelix on day 5 or day 6 of stimulation.

*Administration in the evening:* Treatment with cetrorelix 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 cetrorelix 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 cetrorelix may be delayed in absence of follicular growth, although clinical experience is based on starting cetrorelix on day 5 or day 6 of stimulation.

**4.3 Contraindications**

Cetrorelix 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 (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 cetrorelix 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 316 newborns of women administered cetrorelix for infertility treatments suggest that cetrorelix does not increase the risk of congenital anomalies in the offsprings.

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 (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 cetrorelix. *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 and breast-feeding
Cetrorelix 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**

Cetrorelix 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 cetrorelix 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.

Tabulated 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).

| MedDRA system organ class (SOC) | Common | Uncommon |
|---|---|---|
| Immune system disorders | | Systemic allergic/pseudo-allergic reactions including life-threatening anaphylaxis. |
| Nervous system disorders | | Headache |
| Gastrointestinal disorders | | Nausea |
| Reproductive system and breast disorder | Mild to moderate OHSS (WHO grade I or II) can occur which is an intrinsic risk of the stimulation procedure (see section 4.4). | Severe OHSS (WHO grade III) |
| General disorders and administration | Local reactions at the | |

| | | |
|---|---|---|
| site conditions | injection site (e.g. erythema, swelling and pruritus) | |

Reporting of suspected adverse reactions
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. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance
Website: www.hpra.ie.

**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**

Mannitol (E 421)
S-Lactic acid
Water for injection

**6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

**6.3 Shelf life**

2 years.

**6.4 Special precautions for storage**

Store in a refrigerator (2 °C - 8 °C).

The unopened product may be stored in the original package at room temperature (not above 25 °C) for up to three months.

**6.5 Nature and contents of container**

The pre-filled syringe presentation consists of:

Type I clear glass barrel (1 ml) affixed with a 27 G ½ inch needle and stoppered with a bromobutyl elastomer plunger stopper. Syringe has a white plunger rod and an automatic safety system.

One pre-filled syringe assembled with a safety device is packed in 1 blister. One blister along with 1 alcohol swab will be packed in a carton.

Multipacks containing 7 pre-filled syringes assembled with safety devices are packed in 7 blisters. 7 blisters along with 7 alcohol swabs are packed in 7 single cartons separately and placed together in the multipack.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

This product must be at room temperature prior to injection. Remove from the refrigerator approximately 30 minutes before use.

The subcutaneous injection is administered in the same way as with a classical syringe. For syringes with safety device system the needle must be oriented away from the user and anyone else who is present. The safety system is activated by pressing firmly on the plunger rod. The protective sleeve will automatically cover the needle and will produce an audible click which

confirms the activation of the device. Immediately, the syringe must be discarded by throwing it into the nearest sharps bin (the needle in). The container lid must be closed tightly and the container placed out of the reach of children.

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

**7 MARKETING AUTHORISATION HOLDER**

Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132JH Hoofddorp
Netherlands

**8 MARKETING AUTHORISATION NUMBER**

PA2050/005/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 12th February 2021
Date of last renewal: 19th November 2025

**10 DATE OF REVISION OF THE TEXT**

June 2025