



# Steps for Self-Injection of Cetrotide®



## Reassurance matters

For nearly 20 years, Cetrotide® has been used in fertility treatment.

### INDICATIONS

#### What are the uses of Cetrotide®?

Cetrotide® blocks the effects of a natural hormone, called gonadotropin-releasing hormone (GnRH). GnRH controls the secretion of another hormone, called luteinizing hormone (LH), which induces ovulation during the menstrual cycle.

Cetrotide® blocks undesirable premature ovulation. Premature ovulation may lead to eggs that are not available for egg retrieval.

### IMPORTANT RISK INFORMATION

#### Who should not use Cetrotide®?

- Patients that are allergic to cetrotorelix acetate, mannitol, or exogenous peptide hormones (medicines similar to Cetrotide®) should not use Cetrotide®.
- If you have had severe allergic reactions to any drugs in a previous IVF cycle, tell your doctor.
- Cetrotide® should not be used in patients who are pregnant, think they might be pregnant, or are breastfeeding.
- Cetrotide® should not be used in patients with kidney disease.

### How to use Cetrotide®

Do not inject Cetrotide® at home until your healthcare provider has taught you the right way to inject it.

Cetrotide® is for injection under the skin of the lower abdomen area, staying at least one inch away from the belly button. Choose a different injection site each day to minimize irritation.

**Please read the following instructions carefully.**

#### PREP:

#### Before you get started



**Cetrotide® must be stored in the refrigerator between 36-46°F. Do not freeze. Keep the packaged tray in the outer carton in order to protect it from light.**



Wash your hands with soap and water to keep the things you use as clean as possible.



Gather everything you need on a clean, flat surface:

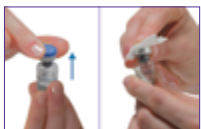
- one vial of powder
- one pre-filled syringe with sterile water (diluent)
- one needle with a **yellow** mark – for injecting the sterile water into the vial and drawing the mixed medicine out from the vial
- one needle with a **gray** mark – for injecting the medicine into your abdomen
- two alcohol swabs

Before starting Cetrotide®, tell your healthcare professional about all your medical conditions. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements

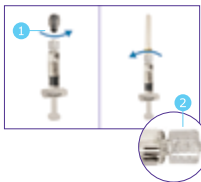
You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088. Or contact EMD Serono at 1-800-283-8088.

**Please see Important Risk Information continued on page 2 and accompanying Full Prescribing Information.**

## Mixing the powder and water to make your medicine



Flip off the plastic cover of the vial. Wipe the aluminum ring and the rubber stopper with an alcohol swab.



Take the injection needle with the **yellow** mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Twist the top off of the needle with the **yellow** mark. Gently twist the cover from the pre-filled syringe to remove, and then twist the yellow needle onto it. Remove the yellow needle cover. It is important to **gently** twist the **1 removable plastic cover** from the syringe to be able to connect AND disconnect the needle(s). Pulling or twisting with too much force may disconnect the **2 affixed acrylic connection tip** and compromise the contents of the syringe.



Push the needle through the center of the rubber stopper of the vial. Inject the water into the vial by slowly pushing down on the plunger of the syringe.



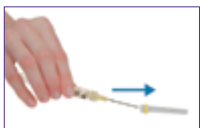
Leave the syringe in the vial. While carefully holding the syringe and vial, swirl gently to mix the powder and water together. When it is mixed, it will look clear and have no particles in it. **Do not shake** or you will create bubbles in your medicine.



Draw the total contents of the vial into the syringe. If liquid is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid.



**It is important to withdraw the entire contents of the vial. The 3 backstop should NOT be removed—it is in place to ensure the plunger in the syringe can't be removed completely and the sterility of the medication isn't compromised.**



Put the cap back on the yellow needle. Gently unscrew the yellow needle from the syringe and lay down the syringe.

**See FAQs for safe disposal of used needles, vial, and syringe.**

## Preparing the injection site and your syringe



Take the injection needle with the **gray** mark and remove its wrapping. Twist the needle on the syringe and remove the cover of the needle.



Invert the syringe and push the plunger until all air bubbles have been pushed out.

**Do not touch the needle or allow the needle to touch any surface.**



Choose an injection site in the lower abdominal area, preferably around, but at least one inch away from the belly button. Choose a different injection site each day to minimize local irritation. Take a second alcohol swab and clean the skin at the injection site and allow alcohol to dry. Inject the prescribed dose as directed by your doctor, nurse or pharmacist.

## Injecting your medicine



With one hand, gently pinch up the previously cleaned skin around the chosen injection site. With the other, hold the syringe like you would hold a pencil.



Slowly push down on the plunger until all of your medication is injected.



Remove the needle from your skin at the same angle and put the cap back on the gray needle so it is safe to be thrown away. Use the syringe and needles only once. Properly dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury). A medical waste container should be used for disposal.

**See FAQs for safe disposal of used needles, vial, and syringe.**

**Do not reuse or share syringes or needles**

### IMPORTANT RISK INFORMATION (continued)

#### What is the most important information I should know before starting Cetrotide®?

- Your doctor will confirm you are not pregnant.

#### What are the possible side effects of Cetrotide®?

Cetrotide® may cause serious side effects including:

- Allergic reactions including anaphylactic reaction with the first dose. Treatment with Cetrotide® is not advised in women with severe allergic conditions.
- Your doctor should review with you the risks and benefits of using Cetrotide®.
- It is not known if Cetrotide® is excreted in human milk. Because the effects of Cetrotide® on nursing mothers or the nursing infant are not known, do not use Cetrotide® if you are breastfeeding.

Common side effects of using Cetrotide® include:

- Mild and short-lasting reactions may occur at the injection site like reddening, itching, and swelling. Nausea and headache have also been reported.

Call your doctor if you have any other side effect or if you are unsure about the effect of this medicine.

These are not all the possible side effects of Cetrotide®. For more information, read the product labeling, and ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**Please see Full Prescribing Information and Patient Leaflet for Cetrotide® provided with this tear pad and in your product carton, or visit online.**

## FAQs

### How do I properly dispose of medicine products?

Used needles, vial, and syringe should be discarded in an FDA-cleared sharps disposal container immediately after use.

If you do not have a sharps container, do not throw away loose needles and vials in your household trashcan.

Instead, use a container that is:

- made of heavy-duty plastic
- able to be closed with a tight-fitting, puncture-resistant lid
- upright and stable during use
- leak resistant
- properly labeled to warn of hazardous waste inside the container

For more information, visit [www.fda.gov/safesharpsdisposal](http://www.fda.gov/safesharpsdisposal).

### What do I do if I have used too much Cetrotide®?

In case of overdosage, contact your doctor immediately to check whether an adjustment of the further ovarian stimulation procedure is required.

### Can I still use my medication if I left it outside in a car during hot or cold weather?

Cetrotide® must be stored away from light and in the refrigerator between 36°F and 46°F.

For more information about storing your medication, call Fertility LifeLines™ support at 1-866-538-7879 or contact your healthcare provider.



### MORE SUPPORT

For more support materials, visit [EMDSeronoFertility.com](http://EMDSeronoFertility.com).

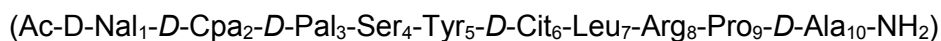
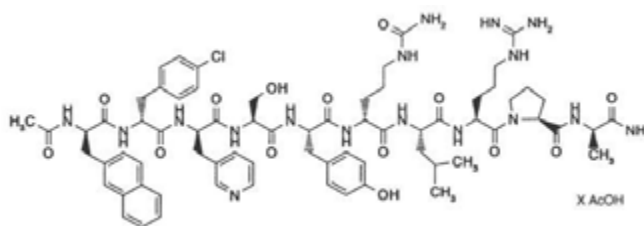
**Cetrotide® 0.25 mg  
(cetrotirelix acetate for injection)**

**FOR SUBCUTANEOUS USE ONLY**

**DESCRIPTION**

Cetrotide® (cetrotirelix acetate for injection) is a synthetic decapeptide with gonadotropin-releasing hormone (GnRH) antagonistic activity. Cetrotirelix acetate is an analog of native GnRH with substitutions of amino acids at positions 1, 2, 3, 6, and 10. The molecular formula is Acetyl-D-3-(2'-naphthyl)-alanine-D-4-chlorophenylalanine-D-3-(3'-pyridyl)-alanine-L-serine-L-tyrosine-D-citrulline-L-leucine-L-arginine-L-proline-D-alanine-amide, and the molecular weight is 1431.06, calculated as the anhydrous free base. The structural formula is as follows:

**Cetrotirelix acetate**



Cetrotide® (cetrotirelix acetate for injection) 0.25 mg is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (pH 5-8), that comes supplied in a 1.0 mL pre-filled syringe. Each vial of Cetrotide® 0.25 mg contains 0.26-0.27 mg cetrotirelix acetate, equivalent to 0.25 mg cetrotirelix, and 54.80 mg mannitol.

**CLINICAL PHARMACOLOGY**

GnRH induces the production and release of luteinizing hormone (LH) and follicle stimulating 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.

Cetrotide® 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 Cetrotide®, which is consistent with an antagonist effect.

The effects of Cetrotide® on LH and FSH are reversible after discontinuation of treatment. In women, Cetrotide® 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 Cetrotide®, duration of action of at least 4 days has been established. A dose of Cetrotide® 0.25 mg every 24 hours has been shown to maintain the effect.

## Pharmacokinetics

The pharmacokinetic parameters of single and multiple doses of Cetrotide® (cetrotide acetate for injection) in adult healthy female subjects are summarized in Table 1.

**Table 1: Pharmacokinetic parameters of Cetrotide® 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
$t_{\max}^{\dagger}$ [h]	1.5 (0.5-2)	1.0 (0.5-1.5)	1.0 (0.5-2)
$t_{1/2}^{\dagger}$ [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]	1.28 <sup>‡</sup>		
Vz* [l/kg]	1.16 <sup>‡</sup>		

$t_{\max}$  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  $AUC_{0-\infty}$ , multiple dose AUCt

CL Total plasma clearance

Vz Volume of distribution

Geometric mean (95% CI<sub>n</sub>),

\* arithmetic mean,

† median (min-max)

‡ Based on iv administration (n=6, separate study 0013)

### Absorption

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

### Distribution

The volume of distribution of Cetrotide® following a single intravenous dose of 3 mg is about 1 l/kg. *In vitro* protein binding to human plasma is 86%.

Cetrotide® 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 Cetrotide® 0.25 mg and 3 mg, plasma concentrations of cetrotide were below or in the range of the lower limit of quantitation on the day of oocyte pick-up and embryo transfer.

### Metabolism

After subcutaneous administration of 10 mg Cetrotide® to females and males, Cetrotide® 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, Cetrotide® was stable against phase I- and phase II-metabolism. Cetrotide® was transformed by peptidases, and the (1-4) peptide was the predominant metabolite.

### Excretion

Following subcutaneous administration of 10 mg cetrotide to males and females, only unchanged cetrotide was detected in urine. In 24 hours, cetrotide 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 cetrotide, while 5-10% was eliminated as cetrotide and the four metabolites in bile. Therefore, only 7-14% of the total dose was recovered as unchanged cetrotide 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.

### Special Populations

Pharmacokinetic investigations have not been performed either in subjects with impaired renal or liver function, or in the elderly, or in children (see PRECAUTIONS).

Pharmacokinetic differences in different races have not been determined.

There is no evidence of differences in pharmacokinetic parameters for Cetrotide® between healthy subjects and patients undergoing controlled ovarian stimulation.

### **Drug-Drug Interactions**

No formal drug-drug interaction studies have been performed with Cetrotide® (see PRECAUTIONS).

### **Clinical Studies**

Seven hundred thirty two (732) patients were treated with Cetrotide® (cetrotide acetate for injection) in five (two Phase 2 dose-finding and three Phase 3) clinical trials. The clinical trial population consisted of Caucasians (95.5%) and Black, Asian, Arabian and others (4.5%). Women were between 19 and 40 years of age (mean: 32). The studies excluded subjects with polycystic ovary syndrome (PCOS), subjects with low or no ovarian reserve, and subjects with stage III-IV endometriosis.

Two dose regimens were investigated in these clinical trials, either a single dose per treatment cycle or multiple dosing. In the Phase 2 studies, a single dose of 3 mg was established as the minimal effective dose for the inhibition of premature LH surges with a protection period of at least 4 days. When Cetrotide® is administered in a multidose regimen, 0.25 mg was established as the minimal effective dose. The extent and duration of LH-suppression is dose dependent.

In the Phase 3 program, efficacy of the single 3 mg dose regimen of Cetrotide® and the multiple 0.25 mg dose regimen of Cetrotide® was established separately in two adequate and well controlled clinical studies utilizing active comparators. A third non-comparative clinical study evaluated only the multiple 0.25 mg dose regimen of Cetrotide®. The ovarian stimulation

treatment with recombinant FSH or human menopausal gonadotropin (hMG) was initiated on day 2 or 3 of a normal menstrual cycle. The dose of gonadotropins was administered according to the individual patient's disposition and response.

In the single dose regimen study, Cetrotide® 3 mg was administered on the day of controlled ovarian stimulation when adequate estradiol levels (400 pg/mL) were obtained, usually on day 7 (range day 5-12). If hCG was not given within 4 days of the 3 mg dose of Cetrotide®, then 0.25 mg of Cetrotide® was administered daily beginning 96 hours after the 3 mg injection until and including the day of hCG administration.

In the two multiple dose regimen studies, Cetrotide® 0.25 mg was started on day 5 or 6 of COS. Both gonadotropins and Cetrotide® were continued daily (multiple dose regimen) until the injection of human chorionic gonadotropin (hCG).

Oocyte pick-up (OPU) followed by *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) as well as embryo transfer (ET) were subsequently performed. The results for Cetrotide® are summarized below in Table 2.

**Table 2: Results of Phase 3 Clinical Studies with Cetrotide® (cetrotide acetate for injection) 3 mg in a single dose (sd) regimen and 0.25 mg in a multiple dose (md) regimen**

Parameter	Cetrotide® 3 mg (sd, active comparator study)	Cetrotide® 0.25 mg (md, active comparator study)	Cetrotide® 0.25 mg (md, non-comparative study)
No. of subjects	115	159	303
hCG administered [%]	98.3	96.2	96.0
Oocyte pick-up [%]	98.3	94.3	93.1
LH-surge [%] (LH ≥ 10 U/L and P* ≥ 1 ng/mL) †	0.0	1.9	1.0
Serum E <sub>2</sub> [pg/ml] at day hCG‡, §	1125 (470-2952)	1064 (341-2531)	1185 (311-3676)
Serum LH [U/L] at day hCG‡, §	1.0 (0.5-2.5)	1.5 (0.5-7.6)	1.1 (0.5-3.5)
No. of follicles ≥ 11 mm at day hCG¶	11.2±5.5	10.8±5.2	10.4±4.5
No. of oocytes: IVF¶ ICSI¶	9.2±5.2 10.0±4.2	7.6±4.3 10.1±5.6	8.5±5.1 9.3±5.9
Fertilization rate: IVF¶	0.48±0.33	0.62±0.26	0.60±0.26

ICSI <sup>¶</sup>	0.66±0.29	0.63±0.29	0.61±0.25
No. of embryos transferred <sup>¶</sup>	2.6±0.9	2.1±0.6	2.7±1.0
Clinical pregnancy rate [%] per attempt	22.6	20.8	19.8
per subject with ET	26.3	24.1	23.3

\* Progesterone

† Following initiation of Cetrotide<sup>®</sup> therapy

‡ Morning values

§ Median with 5th – 95th percentiles

¶ Mean ± standard deviation

In addition to IVF and ICSI, one pregnancy was obtained after intrauterine insemination. In the five Phase 2 and Phase 3 clinical trials, 184 pregnancies have been reported out of a total of 732 patients (including 21 pregnancies following the replacement of frozen-thawed embryos).

In the 3 mg regimen, 9 patients received an additional dose of 0.25 mg of Cetrotide<sup>®</sup> and two other patients received two additional doses of 0.25 mg Cetrotide<sup>®</sup>. The median number of days of Cetrotide<sup>®</sup> multiple dose treatment was 5 (range 1-15) in both studies.

No drug related allergic reactions were reported from these clinical studies.

## INDICATIONS AND USAGE

Cetrotide<sup>®</sup> (cetorelix acetate for injection) is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.

## CONTRAINDICATIONS

Cetrotide<sup>®</sup> (cetorelix acetate for injection) is contraindicated under the following conditions:

1. Hypersensitivity to cetorelix acetate, extrinsic peptide hormones or mannitol.
2. Known hypersensitivity to GnRH or any other GnRH analogs.
3. Known or suspected pregnancy, and lactation (see PRECAUTIONS).
4. Severe renal impairment

## WARNINGS



Cetrotide® (cetorelix acetate for injection) should be prescribed by physicians who are experienced in fertility treatment. Before starting treatment with Cetrotide®, pregnancy must be excluded (see CONTRAINDICATIONS and PRECAUTIONS).

## **PRECAUTIONS**

### **General**

Cases of hypersensitivity reactions, including anaphylactoid reactions with the first dose, have been reported during post-marketing surveillance (see ADVERSE REACTIONS). A severe anaphylactic reaction associated with cough, rash, and hypotension, was observed in one patient after seven months of treatment with Cetrotide® (10 mg/day) in a study 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 Cetrotide® is not advised in women with severe allergic conditions.

### **Information for Patients**

Prior to therapy with Cetrotide® (cetorelix 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 (see ADVERSE REACTIONS). Cetrotide® should not be prescribed if a patient is pregnant.

If Cetrotide® is prescribed to patients for self-administration, information for proper use is given in the Patient Leaflet (see below).

### **Laboratory Tests**

After the exclusion of preexisting conditions, enzyme elevations (ALT, AST, GGT, alkaline phosphatase) were found in 1-2% of patients receiving Cetrotide® 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, Cetrotide® had no notable effects on hormone levels aside from inhibition of LH surges.

### **Drug Interactions**

No formal drug interaction studies have been performed with Cetrotide®.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term carcinogenicity studies in animals have not been performed with cetrorelix acetate. Cetrorelix acetate was not genotoxic *in vitro* (Ames test, HPRT test, chromosome aberration test) or *in vivo* (chromosome aberration test, mouse micronucleus test). Cetrorelix acetate induced polyploidy in CHL-Chinese hamster lung fibroblasts, but not in V79-Chinese hamster lung fibroblasts, cultured peripheral human lymphocytes or in an *in vitro* micronucleus test in the CHL-cell line. Treatment with 0.46 mg/kg cetrorelix acetate for 4 weeks resulted in complete infertility in female rats which was reversed 8 weeks after cessation of treatment.

### **Pregnancy (see CONTRAINDICATIONS)**

Cetrotide® is contraindicated in pregnant women.

When administered to rats for the first seven days of pregnancy, cetrorelix acetate did not affect the development of the implanted conceptus at doses up to 38 µg/kg (approximately 1 times the recommended human therapeutic dose based on body surface area). However, a dose of 139 µg/kg (approximately 4 times the human dose) resulted in a resorption rate and a postimplantation loss of 100%. When administered from day 6 to near term to pregnant rats and rabbits, very early resorptions and total implantation losses were seen in rats at doses from 4.6 µg/kg (0.2 times the human dose) and in rabbits at doses from 6.8 µg/kg (0.4 times the human dose). In animals that maintained their pregnancy, there was no increase in the incidence of fetal abnormalities.

The fetal resorption observed in animals is a logical consequence of the alteration in hormonal levels effected by the antigonadotrophic properties of Cetrotide<sup>®</sup>, which could result in fetal loss in humans as well. Therefore, this drug should not be used in pregnant women.

### **Nursing Mothers**

It is not known whether Cetrotide<sup>®</sup> is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of Cetrotide<sup>®</sup> on lactation and/or the breast-fed child have not been determined, Cetrotide<sup>®</sup> should not be used by nursing mothers.

### **Geriatric Use**

Cetrotide<sup>®</sup> is not intended to be used in subjects aged 65 and over.

### **ADVERSE REACTIONS**

The safety of Cetrotide<sup>®</sup> (cetrotide acetate for injection) in 949 patients undergoing controlled ovarian stimulation in clinical studies was evaluated. Women were between 19 and 40 years of age (mean: 32). 94.0% of them were Caucasian. Cetrotide<sup>®</sup> was given in doses ranging from 0.1 mg to 5 mg as either a single or multiple dose.

Table 3 shows systemic adverse events, reported in clinical studies without regard to causality, from the beginning of Cetrotide<sup>®</sup> treatment until confirmation of pregnancy by ultrasound at an incidence  $\geq 1\%$  in Cetrotide<sup>®</sup> treated subjects undergoing COS.

<b>Table 3: Adverse Events in <math>\geq 1\%</math></b> (WHO preferred term)	<b>Cetrotide<sup>®</sup> N=949</b> <b>% (n)</b>
Ovarian Hyperstimulation Syndrome*	3.5 (33)
Nausea	1.3 (12)
Headache	1.1 (10)

\* Intensity moderate or severe, or WHO Grade II or III, respectively

Local site reactions (e.g. redness, erythema, bruising, itching, swelling, and pruritus) were reported. Usually, they were of a transient nature, mild intensity and short duration. During post-marketing surveillance, cases of mild to moderate Ovarian Hyperstimulation syndrome and

infrequent cases of hypersensitivity reactions including anaphylactoid reactions have been reported.

Two stillbirths were reported in Phase 3 studies of Cetrotide®.

### **Congenital Anomalies**

Clinical follow-up studies of 316 newborns of women administered Cetrotide® 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 defect and another child with bilateral congenital glaucoma.

Four pregnancies that resulted in therapeutic abortion in Phase 2 and Phase 3 controlled ovarian stimulation studies 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, hemangiomas, and QT syndrome.

The causal relationship between the reported anomalies and Cetrotide® is unknown. Multiple factors, genetic and others (including, but not limited to ICSI, IVF, gonadotropins, and progesterone) make causal attribution difficult to study.

### **OVERDOSAGE**

There have been no reports of overdosage with Cetrotide® 0.25 mg or 3 mg in humans. Single doses up to 120 mg Cetrotide® have been well tolerated in patients treated for other indications without signs of overdosage.

### **DOSAGE AND ADMINISTRATION**

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. Cetrotide® (cetrotirelix acetate for injection) 0.25 mg may be administered subcutaneously once daily during the early- to mid-follicular phase.

Cetrotide® 0.25 mg 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).

### **Administration**

Cetrotide® 0.25 mg can be administered by the patient herself after appropriate instructions by her doctor.

### **Directions for using Cetrotide® 0.25 mg with the enclosed needles and pre-filled syringe:**

1. Wash hands thoroughly with soap and water.
2. Flip off the plastic cover of the vial and wipe the aluminum ring and the rubber stopper with an alcohol swab.
3. Twist the injection needle with the yellow mark (20 gauge) on the pre-filled syringe.
4. Push the needle through the center of the rubber stopper of the vial and slowly inject the solvent into the vial.
5. Leaving the syringe in the vial, gently swirl the vial until the solution is clear and without residues. Avoid forming bubbles.
6. 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 of the vial.
7. Replace the needle with the yellow mark by the injection needle with the grey mark (27 gauge).
8. Invert the syringe and push the plunger until all air bubbles have been expelled.

9. Choose an injection site in the lower abdominal area, preferably around, but staying at least one inch away from the navel. Choose a different injection site each day to minimize local irritation. Use a second alcohol swab to clean the skin at the injection site and allow alcohol to dry. Gently pinch up the skin surrounding the site of injection.
10. Inject the prescribed dose as directed by your doctor, nurse or pharmacist.
11. Use the syringe and needles only once. Dispose of the syringe and needles properly after use. If available, use a medical waste container for disposal.

## **HOW SUPPLIED**

Cetrotide® (cetorelix acetate for injection) 0.25 mg is available in a carton of one packaged tray (NDC 44087-1225-1).

Each packaged tray contains: one glass vial containing 0.26 - 0.27 mg cetorelix acetate (corresponding to 0.25 mg cetorelix), one pre-filled glass syringe with 1 mL of Sterile Water for Injection, USP (pH 5-8), one 20 gauge needle (yellow) and one 27 gauge needle (grey).

## **Storage**

Store Cetrotide® 0.25 mg refrigerated, 2-8°C (36-46°F). Store the packaged tray in the outer carton in order to protect from light.

## **Rx only**

Manufactured for:

EMD Serono, Inc, Rockland, MA 02370, USA

**May 2018**

## **Patient Leaflet**

### **Cetrotide® 0.25 mg**

Active ingredient: cetrorelix acetate

### **Summary**

Cetrotide® blocks the effects of a natural hormone, called gonadotropin-releasing hormone (GnRH). GnRH controls the secretion of another hormone, called luteinizing hormone (LH), which induces ovulation during the menstrual cycle. During hormone treatment for ovarian stimulation, premature ovulation may lead to eggs that are not suitable for fertilization.

Cetrotide® blocks such undesirable premature ovulation.

### **Uses**

Cetrotide® is used to prevent premature ovulation during controlled ovarian stimulation.

### **General Cautions**

Do not use Cetrotide® if you

- have kidney disease
- are allergic to cetrorelix acetate, mannitol or exogenous peptide hormones (medicines similar to Cetrotide®) or
- are pregnant, or think that you might be pregnant, or if you are breast-feeding.

Consult your doctor before taking Cetrotide® if you have had severe allergic reactions.

### **Proper Use**

Ovarian stimulation therapy is started on cycle Day 2 or 3. Cetrotide® 0.25 mg is injected under the skin once daily, as directed by your physician. When an ultrasound examination shows that you are ready, another drug (hCG) is injected to induce ovulation.

***How should you use Cetrotide®?***

You may self-inject Cetrotide® after special instruction from your doctor.

To fully benefit from Cetrotide®, please read carefully and follow the instructions given below, unless your doctor advises you otherwise.

Cetrotide® is for injection under the skin of the lower abdominal area, preferably around, but staying at least one inch away from the belly button. Choose a different injection site each day to minimize local irritation.

Dissolve Cetrotide® powder only with the water contained in the pre-filled syringe. Do not use a Cetrotide® solution if it contains particles or if it is not clear.

Before you inject Cetrotide® yourself, please read the following instructions carefully:

**Directions for using Cetrotide® 0.25 mg with the enclosed needles and pre-filled syringe:**

1. Wash your hands thoroughly with soap and water.



2. On a clean flat surface, lay out everything you need (one vial of powder, one pre-filled syringe, one injection needle with a yellow mark, and one injection needle with a grey mark).



3. Flip off the plastic cover of the vial. Wipe the aluminum ring and the rubber stopper with an alcohol swab.



4. Take the injection needle with the yellow mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Twist the needle on the syringe and remove the cover of the needle.





5. Push the needle through the center of the rubber stopper of the vial. Inject the water into the vial by slowly pushing down on the plunger of the syringe.



6. Leave the syringe in the vial. While carefully holding the syringe and vial, swirl gently to mix the powder and water together. When it is mixed, it will look clear and have no particles in it. Do not shake or you will create bubbles in your medicine.



7. Draw the total contents of the vial into the syringe. If liquid is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.



8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Twist the needle on the syringe and remove the cover of the needle.



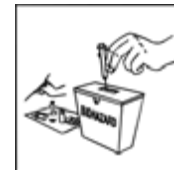
9. Invert the syringe and push the plunger until all air bubbles have been pushed out. Do not touch the needle or allow the needle to touch any surface.



10. Choose an injection site in the lower abdominal area, preferably around, but at least one inch away from the belly button. Choose a different injection site each day to minimize local irritation. Take a second alcohol swab and clean the skin at the injection site and allow alcohol to dry. Inject the prescribed dose as directed by your doctor, nurse or pharmacist.



11. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury). A medical waste container should be used for disposal.



## **SPECIAL ADVICE**

### ***What do you do if you have used too much Cetrotide®?***

Contact your doctor in case of overdose immediately to check whether an adjustment of the further ovarian stimulation procedure is required.

## **Possible Side Effects**

Mild and short lasting reactions may occur at the injection site like reddening, itching, and swelling. Nausea and headache have also been reported.

Call your doctor if you have any side effect not mentioned in this leaflet or if you are unsure about the effect of this medicine.

## **Storage**

### ***How is Cetrotide® to be stored?***

Store Cetrotide® in a cool dry place protected from excess moisture and heat.

Store Cetrotide® 0.25 mg in the refrigerator at 2-8°C (36-46°F). Keep the packaged tray in the outer carton in order to protect it from light.

***How long may Cetrotide® be stored?***

Do not use the Cetrotide® powder or the pre-filled syringe after the expiration date, which is printed on the labels and on the carton, and dispose of the vial and the syringe properly.

***How long can you keep Cetrotide® after preparation of the solution?***

The solution should be used immediately after preparation.

***Store the medicine out of the reach of children.***

If you suspect that you may have taken more than the prescribed dose of this medicine, contact your doctor immediately. This medicine was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of the information about Cetrotide®. Medicines are sometimes prescribed for uses other than those listed in the Leaflet. If you have any questions or concerns, or want more information about Cetrotide®, contact your doctor or pharmacist.

This Leaflet has been approved by the U.S. Food and Drug Administration.

**September 2018**