CCDS-MK-8761-INJ-082020_SIN

1. NAME OF THE MEDICINAL PRODUCT

Orgalutran® 0.25 mg/0.5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 0.25 mg of ganirelix (INN) in 0.5 ml aqueous solution. The active substance ganirelix is a synthetic decapeptide with high antagonistic activity to the naturally occurring gonadotrophin releasing hormone (GnRH). The amino acids at positions 1, 2, 3, 6, 8 and 10 of the natural GnRH decapeptide have been substituted resulting in N-Ac-D-Nal(2)^{1}, D-pClPhe^{2}, D-Pal(3)^{3}, D-hArg(Et2)^{6}, L-hArg(Et2)^{8}, D-Ala^{10}]-GnRH with a molecular weight of 1570.4.

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colorless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The prevention of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART).

In clinical trials Orgalutran was used with recombinant follicle stimulating hormone (FSH).

4.2 Posology and method of administration

Orgalutran should only be prescribed by a specialist experienced in the treatment of infertility.

Posology

Orgalutran is used to prevent premature LH surges in patients undergoing COH. Controlled ovarian hyperstimulation with FSH may start at day 2 or 3 of menses. Orgalutran (0.25 mg) should be injected subcutaneously once daily, starting in general on day 6 of FSH administration. In high responders an early LH rise may be prevented by starting Orgalutran treatment on day 5. The start of Orgalutran may be delayed in absence of follicular growth.

Orgalutran and FSH should be administered approximately at the same time. However, the preparations should not be mixed and different injection sites are to be used.

FSH dose adjustments should be based on the number and size of growing follicles, rather than on the amount of circulating oestradiol (see section 5.1 Pharmacodynamic properties). Daily treatment with Orgalutran should be continued up to the day that sufficient follicles of adequate size are present. Final maturation of follicles can be induced by administering human chorionic gonadotrophin (hCG). Because of the half-life of ganirelix, the time between two Orgalutran injections as well as the time between the last Orgalutran injection and the hCG injection should not exceed 30 hrs, as otherwise a premature LH surge may occur. Therefore, when injecting Orgalutran in the morning, treatment with Orgalutran should be continued throughout the gonadotrophin treatment period including the day of triggering ovulation. When injecting Orgalutran in the afternoon the last Orgalutran injection should be given in the afternoon prior to the day of triggering ovulation.

Orgalutran has shown to be safe and effective in patients undergoing multiple treatment cycles.

Luteal phase support should be given according to the reproductive medical center's practice.

Method of administration

Orgalutran should be administered subcutaneously, preferably in the upper leg. The injection site should be varied to prevent lipoatrophy. The patient or her partner may perform the injections of Orgalutran themselves, provided that they are adequately instructed and have access to expert advice. Air bubble(s) may be seen in the pre-filled syringe. This is expected, and removal of the air bubble(s) is not needed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any components including dry natural rubber/latex (see sections 6.1 List of excipients and 6.5 Nature and contents of container)
- Hypersensitivity to gonadotropin-releasing hormone (GnRH) or any other GnRH analogue
- Moderate or severe impairment of renal or hepatic function
- Pregnancy or lactation

4.4 Special warnings and precautions for use

Special care should be taken in women with signs and symptoms of active allergic conditions. Cases of hypersensitivity reactions (both generalized and local), have been reported with Orgalutran, as early as with the first dose, during post-marketing surveillance. These events have included anaphylaxis (including anaphylactic shock), angioedema, and urticaria. (See section 4.8 Undesirable effects). If a hypersensitivity reaction is suspected, Orgalutran should be discontinued and appropriate treatment administered. In the

absence of clinical experience, Orgalutran treatment is not advised in women with severe allergic conditions.

The needle shield of this medicinal product contains dry natural rubber/latex which comes into contact with this product and may cause allergic reactions (see sections 4.3 Contraindications and 6.5 Nature and contents of container).

Ovarian hyperstimulation syndrome (OHSS) may occur during or following ovarian stimulation. OHSS must be considered an intrinsic risk of gonadotrophin stimulation. OHSS should be treated symptomatically, e.g., with rest, intravenous infusion of electrolyte solutions or colloids and heparin.

Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.

The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g., maternal age, sperm characteristics) and to the higher incidence of multiple gestations after ART. There are no indications that the use of GnRH antagonists during ART is associated with an increased risk of congenital malformations.

The safety and efficacy of Orgalutran have not been established in women weighing less than 50 kg or more than 90 kg.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions of Orgalutran with other medicines have not been investigated; interactions with commonly used medicinal products can therefore not be excluded.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available.

In animals, exposure to ganirelix at the time of implantation resulted in litter resorption (see section 5.3 Preclinical safety data). The relevance of these data for humans is unknown.

It is not known whether ganirelix is excreted in breast milk.

The use of Orgalutran is contraindicated during pregnancy and lactation. (see section 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

The effects of Orgalutran on ability to drive and use machines have not been studied.

4.8 Undesirable effects

General disorders and administration site conditions.

Orgalutran may cause a local skin reaction at the site of injection (predominantly redness, with or without swelling). In clinical studies, one hour after injection, the incidence of at least one moderate or severe local skin reaction per treatment cycle, as reported by patients, was 12% in Orgalutran treated patients and 25% in patients treated subcutaneously with a GnRH agonist. The local reactions generally disappear within 4 hours after administration. Malaise was reported in 0.3% of patients.

Immune system disorders.

Very rarely, post-marketing cases of hypersensitivity reactions (including rash, facial swelling, dyspnea, anaphylaxis (including anaphylactic shock), angioedema, and urticaria) have been reported, as early as with the first dose, among patients administered Orgalutran.

Nervous system disorders.

Headache (0.4%)

Gastrointestinal disorders.

Nausea (0.5%)

Other reported undesirable effects are related to the controlled ovarian hyperstimulation treatment for ART, notably pelvic pain, abdominal distension, OHSS, ectopic pregnancy and spontaneous abortion (see also section 4.4 “Special warnings and special precautions for use” of this SmPC).

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action. In case of overdose, Orgalutran treatment should be (temporarily) discontinued.

No data on acute toxicity of Orgalutran in humans are available but it is unlikely that toxic effects will occur. Clinical studies with subcutaneous administration of Orgalutran at single doses up to 12 mg did not show systemic undesirable effects. In acute toxicity studies in rats and monkeys non-specific toxic symptoms were only observed after intravenous administration of ganirelix over 1 and 3 mg/kg, respectively.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-gonadotrophin-releasing hormones; ATC code: H01CC01.

Orgalutran is a GnRH antagonist, which modulates the hypothalamic-pituitary-gonadal axis by competitive binding to the GnRH receptors in the pituitary gland. As a result a rapid, profound, reversible suppression of endogenous gonadotrophins occurs, without initial stimulation as induced by GnRH agonists. Following administration of multiple doses of 0.25 mg Orgalutran to female volunteers serum LH, FSH and E_2 concentrations were maximally decreased by 74%, 32% and 25% at 4, 16 and 16 hours after injection, respectively. Serum hormone levels returned to pre-treatment values within two days after the last injection.

In patients undergoing controlled ovarian stimulation the median duration of Orgalutran treatment was 5 days. During Orgalutran treatment the average incidence of LH rises (>10 IU/l) with concomitant progesterone rise (>1 ng/ml) was 1.2% compared to 0.8% during GnRH agonist treatment. Early LH rises, prior to the start of Orgalutran at day 6 of stimulation, did occur especially in high responders, but did not affect the clinical outcome. In these patients LH production was rapidly suppressed after the first Orgalutran administration.

In controlled studies of Orgalutran, using a long protocol of GnRH agonist as a reference, treatment with the Orgalutran regimen resulted in a faster follicular growth during the first days of stimulation but the final cohort of growing follicles was slightly smaller and produced on average less estradiol. This different pattern of follicular growth requires that FSH dose adjustments are based on the number and size of growing follicles, rather than on the amount of circulating estradiol.

5.2 Pharmacokinetic properties

After a single subcutaneous administration of 0.25 mg, serum levels of ganirelix rise rapidly and reach peak levels (C_{max}) of approximately 15 ng/ml within 1 to 2 hours (t_{max}). The elimination half-life ($t_{½}$) is approximately 13 hours and clearance is approximately 2.4 l/h. Excretion occurs via feces

(approximately 75%) and urine (approximately 22%). The bioavailability of Orgalutran following subcutaneous administration is approximately 91%.

Pharmacokinetic parameters after multiple subcutaneous dosing of Orgalutran (once daily injection) were similar to those after a single subcutaneous dose. After repeated dosing 0.25 mg/day steady-state levels of approximately 0.6 ng/ml were reached within 2 to 3 days.

Pharmacokinetic analysis indicates an inverse relationship between bodyweight and serum concentrations of Orgalutran.

Metabolite profile:
The major circulating component in plasma is ganirelix. Ganirelix is also the main compound found in urine. Feces only contain metabolites. The metabolites are small peptide fragments formed by enzymatic hydrolysis of ganirelix at restricted sites. The metabolite profile of Orgalutran in humans was similar to that found in animals.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on safety pharmacology, repeated dose toxicity and genotoxicity.

Reproduction studies carried out with ganirelix at doses of 0.1 to 10 µg/kg/day subcutaneously in the rat and 0.1 to 50 µg/kg/day subcutaneously in the rabbit showed increased litter resorption in the highest dose groups. No teratogenic effects were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid,
Mannitol,

Water for injections.
The pH may have been adjusted with sodium hydroxide and acetic acid.

6.2 Incompatibilities

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

6.3 Shelf life

Refer to outer carton.

6.4 Special precautions for storage

Do not freeze.

Store between 2°C and 30°C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Disposable pre-filled syringes (siliconised Type I glass), containing 0.5 ml of sterile, ready for use, aqueous solution closed with a rubber piston that does not contain latex. Each pre-filled syringe is affixed with a needle **closed by a needle shield of dry natural rubber/latex which comes into contact with this product**. (See sections 4.3 Contraindications and 4.4 Special warnings and precautions for use.)

Supplied in cartons containing 1 or 5 pre-filled syringes.

6.6 Special precautions for handling and disposal

Inspect the solution before use. It must only be used if it is clear and without particulate matter. Any unused product or waste material should be disposed of in accordance with local requirements.

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