

## 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 in 0.5 ml aqueous solution. The active substance ganirelix (INN) 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)<sup>1</sup>, D-pClPhe<sup>2</sup>, D-Pal(3)<sup>3</sup>, D-hArg(Et2)<sup>6</sup>, L-hArg(Et2)<sup>8</sup>, D-Ala<sup>10</sup>]-GnRH with a molecular weight of 1570.4.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless aqueous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

In clinical trials Orgalutran was used with recombinant human 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 on day 6 of FSH administration. The start of Orgalutran may be delayed in absence of follicular growth, although clinical experience is based on starting Orgalutran on day 6 of FSH. 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). 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.

The need for luteal phase support in cycles using Orgalutran has not been studied. In clinical trials, luteal phase support was given according to study centres' practice.

Subjects with renal or hepatic impairment: There is no experience of the use of Orgalutran in subjects with renal or hepatic impairment. Therefore, specific dose recommendations cannot be given (see section 4.3).

#### *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.

### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to gonadotrophin-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. In the absence of clinical experience, Orgalutran treatment is not advised in women with severe allergic conditions.

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.

The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and an increased incidence of multiple gestations. In clinical trials investigating more than 1000 newborns it has been demonstrated that the incidence of congenital malformations in children born after COH treatment using Orgalutran is comparable with that reported after COH treatment using a GnRH agonist.

The safety and efficacy of Orgalutran have not been established in women weighing less than 50 kg or more than 90 kg (see also section 5.1 and 5.2).

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

The possibility of interactions with commonly used medicinal products, including histamine liberating products, cannot be excluded.

### **4.6 Pregnancy and lactation**

There are no adequate data from the use of ganirelix in pregnant women. In animals, exposure to ganirelix at the time of implantation resulted in litter resorption (see section 5.3). 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).

#### **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed.

#### **4.8 Undesirable effects**

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 once a 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. Adverse reactions for Orgalutran are all uncommon (<1%). The incidences as reported in clinical trials are: nausea (0.5%), headache (0.4%) and malaise (0.3%).

Very rarely cases of hypersensitivity reactions including various symptoms such as rash, facial swelling and dyspnoea have been reported among patients administered Orgalutran with FSH. Worsening of a pre-existing eczema has been reported in one subject after the first Orgalutran dose.

Other reported undesirable effects are related to the controlled ovarian hyperstimulation treatment for ART, notably pelvic pain, abdominal distension, OHSS (see also section 4.4), ectopic pregnancy and spontaneous abortion.

#### **4.9 Overdose**

Overdose 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. 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 such as hypotension and bradycardia 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<sub>2</sub> 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. There was a tendency towards an increased incidence of LH and progesterone rises in women with a higher body weight (>80 kg), but no effect on clinical outcome was observed. However, based on the small number of patients treated so far, an effect can not be excluded. 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 oestradiol. 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 oestradiol.

## **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 ( $t_{1/2}$ ) is approximately 13 hours and clearance is approximately 2.4 l/h. Excretion occurs via faeces (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. Faeces 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**

2 years

## **6.4 Special precautions for storage**

Do not freeze.

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. Each pre-filled syringe is affixed with a needle closed by a needle shield of natural rubber.

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

Not all pack sizes may be marketed

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

Inspect the syringe before use. Use only syringes with clear, particle-free solutions and from undamaged containers.

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

### **7. MARKETING AUTHORISATION HOLDER**

N.V. Organon, Kloosterstraat 6, Postbus 20, 5340 BH Oss, The Netherlands

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/00/130/001, 1 pre-filled syringe

EU/1/00/130/002, 5 pre-filled syringes

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

Date of first authorisation: 17 May 2000

Date of last renewal: 17 May 2005

### **10. DATE OF REVISION OF THE TEXT**