

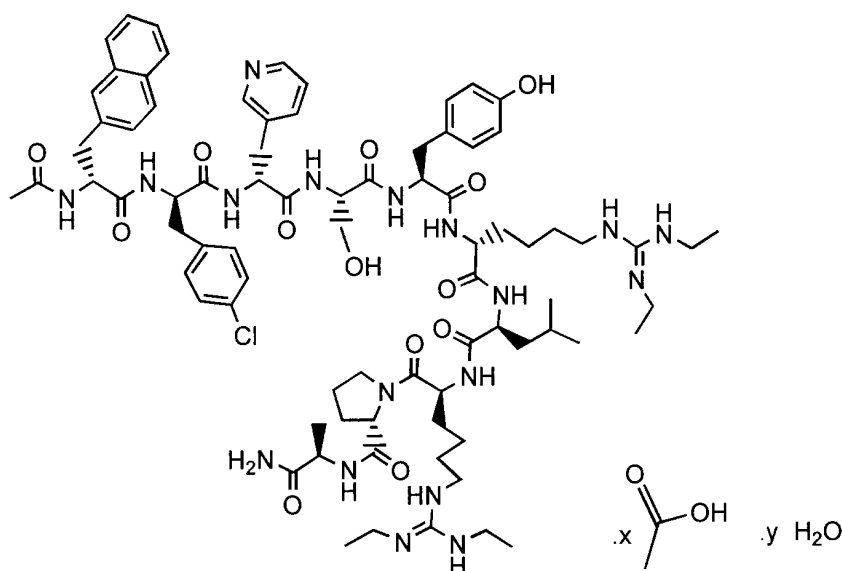
PRODUCT INFORMATION

Orgalutran

(i) NAME OF THE MEDICINE

Orgalutran 250 µg/0.5 mL solution for injection

Orgalutran contains the synthetic decapeptide ganirelix (INN) as its acetate salt, with high antagonistic activity to the naturally occurring gonadotropin 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 Ac-D-Nal-D-4-Cl-Phe-D-Pal-L-Ser-L-Tyr-diEt-hArg-L-Leu-diEt-hArg-L-Pro-D-Ala-NH₂ with a molecular weight of 1570.4 (anhydrous free base).



Molecular formula C₈₀H₁₁₃N₁₈O₁₃Cl. xCH₃CO₂H. yH₂O, hydrated salt where 2 ≤ x ≤ 3 and y ≤ 10.
CAS number: 124904-93-4 (free base); 129311-55-3 (acetate)

(ii) DESCRIPTION

Orgalutran is presented as a sterile, ready for use, clear and colourless aqueous solution intended for subcutaneous administration. Each prefilled syringe contains 250 µg ganirelix (as acetate) in 0.5 mL.

The solution for injection also contains acetic acid, mannitol and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

(iii) PHARMACOLOGY

Pharmacodynamic properties

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

Orgalutran is a GnRH antagonist, which modulates the hypothalamic-pituitary-gonadal axis by competitively binding to the GnRH receptors in the pituitary gland. As a result a rapid, reversible suppression of endogenous gonadotropins occurs, without initial stimulation as induced by GnRH agonists. The inhibitory effect of Orgalutran on the release of LH is more pronounced than on FSH.

When LH has started to rise prior to the first administration of Orgalutran, a premature LH surge can still be prevented.

Important features of the GnRH-antagonist regimen:

- within a few hours suppression of gonadotropin release due to GnRH receptor blockade
- Orgalutran treatment is restricted to those days when a premature LH surge may occur. Therefore, the overall duration of treatment is only several days.
- less suppression of endogenous FSH and therefore less FSH required
- recovery of pituitary functioning within two days following discontinuation of the treatment
- the competitive mode of action of Orgalutran may allow the administration of a GnRH agonist instead of hCG to trigger ovulation, which is especially relevant for patients at risk of developing OHSS
- generally, oestradiol levels are lower (though remaining above natural cycle levels) compared to the relatively high levels in the agonist regimen

Pharmacokinetics

After a single subcutaneous administration of 250 µg, serum levels of ganirelix rise rapidly and reach peak levels (C_{max}) of approximately 15 ng/mL within 1 to 2 hrs (t_{max}). The elimination half-life ($t_{1/2}$) is approximately 13 hrs and clearance is approximately 2.4 L/h. 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.

Metabolite profile:

The major circulating component in plasma is ganirelix. Ganirelix is also the main compound found in urine and faeces only contained metabolites.

Distribution and excretion:

The mean (SD) volume of distribution of Orgalutran in healthy females following intravenous administration of a single 250 µg dose is approximately 44 (± 11) liters. *In vitro* protein binding to human plasma is approximately 82%.

In a radiolabelled study (N=3), Orgalutran was excreted via faeces (approximately 75%) and urine (approximately 22%).

(iv) CLINICAL TRIALS

The efficacy of Orgalutran (ganirelix acetate) was established in three clinical studies. In these studies, the administration of exogenous recombinant FSH [Puregon (follitropin beta for injection)] was initiated on the morning of Day 2 or 3 of a natural menstrual cycle. Orgalutran was administered on the morning of Day 7 or 8 (Day 6 of recombinant FSH administration). The dose of recombinant FSH administered was adjusted according to individual responses starting on the day of initiation of Orgalutran. Both recombinant FSH and Orgalutran were continued daily until at least three follicles were 17 mm or greater in diameter at which time hCG [Pregnyl (chorionic gonadotropin for injection)] was administered. Following hCG administration, Orgalutran and recombinant FSH administration were discontinued. Oocyte retrieval, followed by *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI), was subsequently performed.

In a multicenter, double blind, randomized, dose-finding study (protocol 38602), Orgalutran doses ranging from 62.5 µg to 2000 µg and recombinant FSH were administered to 332 patients undergoing COH for IVF. The results of the selected dose (250 µg) are summarized in the table below.

Two multicentre, open-label, randomized studies (protocol 38607 and 103-001) were conducted in which follicular phase treatment with Orgalutran 250 µg was studied using a GnRH agonist as a reference treatment. A total of 661 subjects were treated with Orgalutran by subcutaneous injection once daily starting on Day 6 of recombinant FSH treatment. Recombinant FSH was maintained at 150 IU or 225 IU in the 38607 and 103-001 study, respectively for the first 5 days of ovarian stimulation

and was then adjusted by the investigator on the sixth day of gonadotropin use according to individual responses. The results for the Orgalutran arm are summarized in the table below.

Results from three multicentre double-blind (38602) or open-label (38607, 103-001), randomized studies:

	Protocol 38602	Protocol 38607	Protocol 103-001
No. subjects treated	70	463	198
Duration of GnRH analog (days) ^{§¶}	4.9(1.7)	5.4(2.0)	4.7(2.1)
Duration of recombinant FSH (days) ^{§¶}	9.8(1.7)	9.6(2.0)	9.0(2.1)
Serum E ₂ (pg/mL) on day of hCG [‡] 5 th -95 th percentiles	1160 384-3910	1190 373-3105	2001 950-4394
Serum LH (mIU/mL) on day of hCG [‡] 5 th -95 th percentiles	1.7 <0.25-6.4	1.6 0.6-6.9	1.7 0.4-7.6
No. of subjects with LH rise \geq 10 mIU/mL [*]	1	13	7
No. of follicles >11mm ^{¶§}	11.4(4.95)	10.7(5.3)	12.3(5.8)
No. of subjects with oocyte retrieval	63	440	186
No. of oocytes [¶]	10.0(5.4)	8.7(5.6)	11.67(6.7)
Fertilization rate (%)	56.1	62.1	62.4
No. subjects with ET [†]	62	399	178
No. of embryos transferred [¶]	2.4(0.86)	2.2(0.6)	2.9(0.5)
No. of embryos [¶]	5.4(4.4)	6.0(4.5)	6.9(4.1)
Ongoing pregnancy rate ^{Ω§}			
per attempt, n (%)	23(33.8)	94(20.3) ^λ	61(30.8)
per transfer, n (%)	23(37.1)	93(23.3)	61(34.3)
Implantation rate (%) [¶]	21.9(31)	15.7(29)	21.1(30.4)

* Following initiation of Orgalutran therapy

‡ Median values

§ Restricted to subjects with hCG injection

¶ Mean (standard deviation)

† ET: Embryo Transfer

Ω As evidenced by ultrasound at 12-16 weeks following ET

λ Includes one patient who achieved pregnancy with intrauterine insemination.

Some centres were limited to the transfer of \leq 2 embryos based on local practice standards

In subjects administered Orgalutran 250 µg, a premature LH surge prior to hCG administration, (LH rise \geq 10 mIU/mL with a significant rise in serum progesterone > 2 ng/mL, or a significant decline in serum oestradiol) occurred in less than 1% of subjects.

In case of high ovarian response, as assessed by the number and size of growing follicles and/or the amount of circulating estradiol, either as a result of a high FSH exposure in the early follicular phase or as a result of high ovarian responsiveness, premature LH rises may occur earlier than day 6 of stimulation. Initiation of Orgalutran treatment on day 5 can effectively prevent these premature LH rises without compromising the clinical outcome.

(v) INDICATIONS

For the prevention of premature luteinisation and ovulation in patients undergoing controlled ovarian stimulation, followed by oocyte pick up and assisted reproductive techniques.

(vi) CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Hypersensitivity to GnRH or any other GnRH analogue
- Pregnancy or lactation
- Moderate to severe renal impairment and hepatic impairment

(vii) PRECAUTIONS

Special care should be taken in women with signs and symptoms of active allergic conditions. Cases of hypersensitivity reactions, have been reported, as early as with the first dose, during post-marketing surveillance (see ADVERSE EFFECTS). Use of Orgalutran in patients with active allergic symptoms has not been investigated. Administration of Orgalutran is not advised to patients with currently severe allergic symptoms. Patients should be advised to contact the attending physician before administering the next injection in case a general or an extensive local allergic reaction occurs.

The packaging of Orgalutran contains natural rubber latex which may cause allergic reactions (see PRESENTATION).

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

Congenital Abnormalities

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 amongst other factors, to differences in parental characteristics (e.g. maternal age, sperm characteristics) and by the higher incidence of multiple gestations after ART. In clinical trials investigating more than 1000 newborns it has been demonstrated that the incidence of congenital malformation in children born after Controlled Ovarian Hyperstimulation (COH) treatment using Orgalutran is comparable with that reported after COH treatment using a GnRH agonist.

Carcinogenicity, mutagenicity and impairment of fertility

Long term carcinogenicity studies with ganirelix have not been carried out. Ganirelix showed no evidence of genotoxicity in assays for gene mutation in bacterial or mammalian cells. Ganirelix was not clastogenic in tests for chromosomal damage in Chinese hamster ovary cells *in vitro* and for micronucleus formation in mice *in vivo*.

Ganirelix treatment of female rats resulted in reversible impairment of mating and fertility at a subcutaneous dose of 2.5 µg/kg/day, and reversible cessation of mating was seen in males treated with a subcutaneous dose of 0.1 mg/kg/day.

Use in Pregnancy (Category D).

Orgalutran is not intended to be used during pregnancy (see Contraindications). No clinical data on exposed pregnancies are available.

Studies in animals have indicated that ganirelix increased the incidence of total fetal resorptions when administered to pregnant rats and rabbits during the period of organogenesis, at respective doses of 10 µg/kg/day and 30 µg/kg/day (approximately 0.4 and 3 times the human dose, based on body surface area). The effects on fetal resorption are logical consequences of the alteration in hormonal levels brought about by the antigonadotrophic properties of Orgalutran and could result in fetal loss in humans. There was no increase in fetal abnormalities. No treatment related changes in fertility, physical, or behavioural characteristics were observed in the offspring of female rats treated with ganirelix during pregnancy and lactation.

Use in lactation. Orgalutran should not be used by lactating women (see Contraindications). It is not known whether ganirelix is excreted into animal or human breast milk. Subcutaneous ganirelix doses of 2.5 µg/kg/day given to lactating rats did not result in impairment of postnatal development of the offspring.

(viii) INTERACTIONS WITH OTHER MEDICINES

In clinical studies, interactions of Orgalutran with other medicines have not been investigated. Therefore, interactions with commonly used medicinal products can not be excluded.

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

Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

(ix) ADVERSE EFFECTS

General disorders and administrative site conditions

Orgalutran may cause a skin reaction (in 10% - 15% of the patients moderate or severe redness with or without swelling was reported) at the site of injection, which normally disappears 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 various symptoms such as rash, facial swelling and dyspnoea) 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 adverse events are rather related to the controlled ovarian hyperstimulation treatment for assisted reproduction technique (ART) than to Orgalutran (e.g. pelvic pain, abdominal distension, ovarian hyperstimulation syndrome (OHSS), ectopic pregnancy and spontaneous abortion).

(x) DOSAGE AND ADMINISTRATION

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

Dosage

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 from day 5 or day 6 of FSH administration depending on the level of ovarian response. Orgalutran should not be mixed with FSH but both preparations should be administered approximately at the same time. 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 hCG. Because of the half life of ganirelix, the time between two Orgalutran injections and between the last Orgalutran injection and the hCG injection should not exceed 30 hrs, as otherwise a premature LH surge may occur.

Method of administration

Inspect the solution before use. It must only be used if it is clear and without particulate matter.

Orgalutran should be administered subcutaneously. 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.

(xi) OVERDOSAGE

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. Clinical studies with subcutaneous administration of Orgalutran at single doses up to 12 mg did not show systemic side-effects. Clinical signs of systemic toxicity including collapse, laboured respiration and inactivity in rats or facial flushing in monkeys were observed after intravenous administration of ganirelix at 2.0 and 3.0 mg/kg,

respectively. Blood pressure was also reduced by about 50% in rats treated with an intravenous ganirelix dose of 0.9 mg/kg.

(xii) PRESENTATION AND STORAGE CONDITIONS

Orgalutran is supplied in disposable prefilled syringes (siliconised Type I glass), containing 250 µg ganirelix/0.5 mL. Each prefilled syringe is affixed with a needle **closed by a needle shield of natural rubber latex** (see PRECAUTIONS).

Boxes of Orgalutran contain 1 or 5 prefilled syringes.

Storage and Shelf-life

36 months when stored at room temperature below 30°C, in the original package. Do not freeze as the syringe may break.

Instructions for use and handling and disposal

This product is for single use only. Discard any remaining contents.

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

(xiii) NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
Australia

(xiv) POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

(xv) DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

18 March 2001

Australian Registration No.: AUSTR 74931

(xvi) DATE OF MOST RECENT AMENDMENT

25 September 2014