PRODUCT MONOGRAPH

ORGALUTRAN®

(Ganirelix Acetate Injection)

250 mcg ganirelix/0.5 ml

Gonadotropin-releasing hormone (GnRH) antagonist

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Date of Revision:
August 8, 2018

Control # 216695

PRODUCT MONOGRAPH

NAME OF DRUG

Orgalutran®
(Ganirelix Acetate Injection)
250 mcg ganirelix/0.5 ml

THERAPEUTIC CLASSIFICATION

Gonadotropin-releasing hormone (GnRH) antagonist

ACTIONS AND CLINICAL PHARMACOLOGY

The pulsatile release of GnRH stimulates the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The frequency of LH pulses in the mid and late follicular phase is approximately 1 pulse per hour. These pulses can be detected as transient rises in serum LH. At midcycle, a large increase in GnRH release results in an LH surge. The midcycle LH surge initiates several physiologic actions including: resumption of meiosis in the oocyte, ovulation and luteinization. Luteinization results in a rise in serum progesterone with an accompanying decrease in estradiol levels.

Orgalutran® (ganirelix acetate injection) acts by competitively blocking the GnRH receptors on the pituitary gonadotroph and subsequent transduction pathway. It induces a rapid, reversible suppression of gonadotropin secretion. The suppression of pituitary LH secretion by Orgalutran is more pronounced than that of FSH. An initial release of endogenous gonadotropins has not been detected with Orgalutran, which is consistent with a rapid antagonistic effect.

Orgalutran may be displaced during competition for the GnRH receptor by GnRH agonists. This may result in the stimulation of significant LH release and, thus, trigger an LH surge. Upon discontinuation of Orgalutran, pituitary LH and FSH levels are fully recovered within 48 hours.

Pharmacokinetics

The pharmacokinetic parameters of single and multiple injections of Orgalutran® (ganirelix acetate injection) in healthy adult females are summarized in Table I. Steady state serum concentrations were reached after 2 to 3 days of treatment. The pharmacokinetics are dose-proportional in the dose range of 125 - 500 mcg.

TABLE I: Mean (SD) pharmacokinetic parameters of 250 mcg of Orgalutran® following a single subcutaneous (SC) injection (n=15) and daily SC injections (n=15) for seven days.

	t_{max} h	$t_{1/2}$ h	C_{max} ng/mL	AUC ng·h/mL	CL L/hr	V_d L
Orgalutran single dose	1.1(0.3)	12.8(4.3)	14.8(3.2)	96(12)	2.4 (0.2)†	43.7(11.4)†
Orgalutran multiple dose	1.1(0.2)	16.2 (1.6)	11.2(2.4)	77.1(9.8)	3.3 (0.4)*	76.5(10.3)

t_{max} Time to maximum concentration
$t_{1/2}$ Elimination half-life
C_{max} Maximum serum concentration
AUC Area under the curve; Single dose: $AUC_{0-\infty}$; multiple dose AUC_{0-24}
V_d Volume of distribution
† Based on intravenous administration
CL Clearance = $Dose/AUC_{0-\infty}$
* Apparent Clearance

Absorption

The geometric mean absolute bioavailability of Orgalutran® following a single 250 mcg subcutaneous injection to healthy female volunteers is 91.1%. Maximum serum concentrations [C_{max} (SD)] following 250 mcg of ganirelix acetate were 14.8 (3.2) and 11.2 (2.4) ng/mL for single and multiple doses, respectively. T_{max} is approximately one hour after subcutaneous injection.

Distribution

The mean (SD) volume of distribution of Orgalutran® in healthy females following intravenous administration of a single 250 mcg dose is 43.7(11.4) liters (L). The apparent volume of distribution (SD) following a SC injection of 250 mcg daily for seven days is 76.5(10.3) L. *In vitro* protein binding to human plasma was 81.9%.

Metabolism

Following intravenous administration of radiolabeled Orgalutran® to healthy female volunteers, Orgalutran was the major compound present in the plasma (50-70% of administered dose) and urine (17.0-18.4% of administered dose) up to 4 hours after a single dose. There was no Orgalutran found in the feces. The 1-4 peptide metabolite of Orgalutran was the primary compound observed in the feces.

Elimination

The elimination half-life [$t_{1/2}$ (SD)] following a single 250 mcg SC dose of Orgalutran® to healthy female subjects was 12.8(4.3) hours. The $t_{1/2}$ (SD) following daily 250 mcg SC doses of Orgalutran for seven days was 16.2(1.6) hours. The apparent clearance (SD) following daily 250 mcg SC doses of Orgalutran for seven days was 3.3(0.4) L/hour. Approximately 90% of radiolabeled Orgalutran was excreted in the urine and feces within 192 hours following a single intravenous dose. On average, 97.2% of the total Orgalutran dose administered was recovered in the feces and urine (75.1% and 22.1%, respectively).

INDICATIONS

Orgalutran® (ganirelix acetate injection) is indicated for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation (COH).

CONTRAINDICATIONS

Orgalutran® (ganirelix acetate injection) is contraindicated under the following conditions:

- Known hypersensitivity to Orgalutran, any of its components including dry natural rubber/latex (see **AVAILABILITY OF DOSAGE FORMS** and **PHARMACEUTICAL INFORMATION/Composition**) or to any similar peptide (such as GnRH or other GnRH analog).
- Known or suspected pregnancy.
- Moderate or severe impairment of hepatic or renal function.

WARNINGS

Orgalutran® (ganirelix acetate injection) should be prescribed by physicians who are experienced in infertility treatment. Before starting treatment with Orgalutran Injection, pregnancy must be excluded. Safe use of Orgalutran during pregnancy has not been established (see CONTRAINDICATIONS).

Orgalutran may cause fetal harm when administered to a pregnant woman. No teratogenic effects were observed in rats or rabbits, although, at higher concentrations (≥10 mcg/kg/day in rats and ≥ 30 mcg/kg/day in rabbits), an increase in the extent of

litter resorption was observed. No treatment related changes in fertility, physical, or behavioral characteristics were observed in the offspring of female rats treated with Orgalutran during pregnancy and lactation. Use of Orgalutran in human pregnancy has not been studied. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

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.

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 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. 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.

PRECAUTIONS

General

Hypersensitivity reactions and acute anaphylactic reactions have been reported with GnRH antagonists, including Orgalutran®. Anti-ganirelix antibody formation has not been reported with the use of Orgalutran® (ganirelix acetate injection). However, antibody formation has been reported with other GnRH analogs.

Use of Orgalutran in patients with signs and symptoms of active allergic conditions has not been evaluated, therefore, special care should be taken for these patients. Very

rare cases of hypersensitivity reactions, including various symptoms such as rash, facial swelling and dyspnea, have been reported during post-marketing surveillance, as early as with the first dose, among patients administered Orgalutran (see ADVERSE EFFECTS, Post-Market Adverse Drug Reactions). In the absence of clinical experience, Orgalutran treatment is not advised in women with severe allergic conditions.

The needle shield of this product contains dry natural rubber/latex which comes into contact with this product and may cause allergic reactions (see CONTRAINDICATIONS, AVAILABILITY OF DOSAGE FORMS and PHARMACEUTICAL INFORMATION/Composition).

Efficacy and safety of Orgalutran have not been established in women weighing > 90 kg or < 50 kg.

Efficacy and safety of Orgalutran have not been studied in women for more than 3 consecutive cycles.

Laboratory Tests

The only relevant abnormal laboratory value was a neutrophil count ≥ 8.3 (*10^9/L) in 11.9% of the subjects. In addition, downward shifts within the Orgalutran® group were observed for hematocrit and total bilirubin. The clinical significance of these findings was not determined.

Drug Interactions

Formal *in vivo* or *in vitro* drug-drug interaction studies have not been conducted. Since Orgalutran® can suppress the secretion of pituitary gonadotropins, dose adjustments of exogenous gonadotropins may be necessary when used during COH.

Nursing Mothers

Orgalutran® Injection should not be used by lactating women. It is not known whether this drug is excreted in human milk.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Orgalutran® did not include a sufficient number of subjects aged 65 and over.

ADVERSE EFFECTS

The safety of Orgalutran® (ganirelix acetate injection) was evaluated in two randomized, parallel-group, multicenter controlled clinical studies. Treatment duration for Orgalutran ranged from 1 to 14 days. Table II represents maternal adverse events (AEs) from first day of Orgalutran administration until confirmation of pregnancy by ultrasound at an incidence of ≥1% in Orgalutran treated subjects without regard to causality.

TABLE II: Incidence of common AEs (Incidence ≥1% in Orgalutran®-treated subjects) (All-subjects-treated group).

	Group	
	Orgalutran®	Buserelin
WHO system-organ class	(N=872)	(N=236)
Preferred term	All	All
	n (%)	n (%)
Reproductive disorders, female		
Abdominal pain-gynecological	38 (4.4)	8 (3.4)
Ovarian hyperstimulation syndrome	19 (2.2)	14 (5.9)
Vaginal bleeding	14 (1.6)	8 (3.4)
Dysmenorrhea	0	8 (3.4)
Central and peripheral nervous system disorders		
Headache	71 (8.1)	23 (9.7)
Dizziness	19 (2.2)	3 (1.3)
Fetal disorders		
Death fetal	29 (3.3)	13 (5.5)
Abortion missed	7 (0.8)	3 (1.3)
Gastro-intestinal system disorders		
Nausea	22 (2.5)	4 (1.7)
Abdominal pain	16 (1.8)	4 (1.7)

Body as a whole - general disorders		
Fever	4 (0.5)	3 (1.3)
Fatigue	23 (2.6)	2 (0.8)
Pain	10 (1.1)	1 (0.4)
Hot flushes	15 (1.7)	3 (1.3)
Respiratory system disorders		
Upper respiratory tract infection	6 (0.7)	4 (1.7)
Rhinitis	9 (1.0)	1 (0.4)
Application site disorders		
Injection site reaction	37 (4.2)	5 (2.1)
Red blood cell disorder		
Anemia	1 (0.1)	3 (1.3)

n = number of subjects with AEs or drug-related AEs and N = total number of subjects in the group.

Post-Market Adverse Drug Reactions

During post-marketing surveillance, very rare cases of hypersensitivity reactions, including various symptoms such as rash, facial swelling and dyspnea, have been reported, as early as with the first dose, among patients administered Orgalutran.

DRUG ABUSE AND DEPENDENCE

There have been no reports of abuse or dependence of Orgalutran® (ganirelix acetate injection).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reports of overdosage with Orgalutran® (ganirelix acetate injection) in humans.

DOSAGE AND ADMINISTRATION

Prior to therapy with Orgalutran® (ganirelix acetate injection), patients should be informed of the length of treatment and monitoring procedures that will be required. The risk of possible reactions to the drug should be discussed (see ADVERSE REACTIONS).

After initiating FSH therapy on Day 2 or 3 of the cycle, Orgalutran (ganirelix acetate

injection) 250 mcg should be administered subcutaneously once daily during the early to mid follicular phase to take advantage of endogenous pituitary FSH secretion and therefore to potentially reduce the requirement for exogenously administered FSH. Treatment with Orgalutran should be continued daily until the day of hCG administration. In normal practice, this period is usually around 5 days, although Orgalutran treatment has ranged from 1 to 19 days in clinical trials. When an appropriate number of follicles of adequate size (≥ 17 mm in diameter) are present, as assessed by ultrasound, final maturation of follicles could be induced by administering hCG.

The time between two Orgalutran® injections as well as between the last Orgalutran® injection and the hCG injection should not exceed 30 hours, otherwise a premature ovulation may occur. Therefore, if the patient normally injects Orgalutran® in the morning, the last of the Orgalutran injections in the series should be given on the same day as the hCG is given. If the patient normally injects Orgalutran® in the afternoon, the last Orgalutran® injection should be given in the afternoon prior to the day the hCG is given.

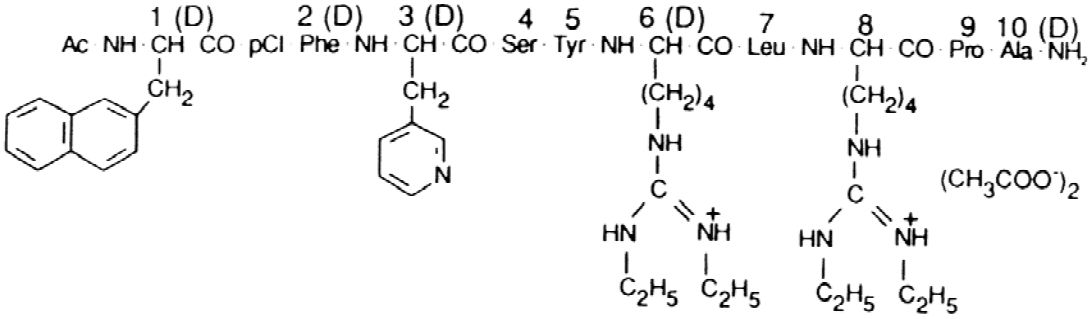
The administration of hCG should be withheld in cases where the ovaries are abnormally enlarged on the last day of FSH therapy. This will reduce the chance of developing OHSS.

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	Ganirelix acetate
Chemical Name:	D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N^6-[(ethylamino)(ethylimino)methyl]-D-lysyl-L-leucyl-N^6-[(ethylamino)(ethylimino)methyl]-L-lysyl-L-prolyl-, diacetate (salt)
Molecular Formula:	$C_{80}H_{113}N_{18}O_{13}Cl$, anhydrous free base $C_{80}H_{113}N_{18}O_{13}Cl \cdot xCH_3CO_2H \cdot yH_20$, hydrated salt, where $2 \leq x \leq 3$ and $y \leq 10$.
Molecular Mass:	1570.4 (anhydrous free base)

Structural Formula:



Physical Form: White to off-white amorphous powder**.** The specific rotation $[\forall]_D^{20}$ of a 1.0% (w/v) solution of ganirelix in 1% acetic acid is between -44° and -52° (based on water and acetic acid free substance).

Composition
Orgalutran® is supplied as a clear, colorless, sterile, ready-to-use, aqueous solution intended for SUBCUTANEOUS administration only. Each pre-filled 0.5 mL syringe contains ganirelix acetate equivalent to 250 mcg ganirelix, glacial acetic acid, mannitol, and water for injection adjusted to pH 5.0 with acetic acid and/or sodium hydroxide.

Stability and Storage Recommendations
Store between 15 - 30°C. Protect from light. SINGLE USE ONLY.

AVAILABILITY OF DOSAGE FORMS

Orgalutran® (ganirelix acetate injection) is supplied in:

Disposable pre-filled, 1 mL glass syringes containing ganirelix acetate equivalent to 250 mcg ganirelix/0.5 mL, closed with a rubber piston that does not contain latex. Each Orgalutran pre-filled syringe is affixed with a 27 gauge x 1/2 inch needle (**closed by a needle shield of dry natural rubber/latex which comes into contact with this product**) (see CONTRAINDICATIONS and PRECAUTIONS).

Available as a single syringe.

The packaging of this product contains natural rubber latex which may cause allergic reactions (see PRECAUTIONS).

INFORMATION FOR THE CONSUMER

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ORGALUTRAN® IS USED FOR

Orgalutran® is used to prevent the premature LH surges in women undergoing Controlled ovarian hyperstimulation (COH). Orgalutran allows the release of an egg to be controlled so that it occurs at an optimal time for pregnancy to occur.

2. WHAT ORGALUTRAN® DOES:

The active ingredient in Orgalutran® is ganirelix acetate, which is a gonadotrophin-releasing hormone (GnRH) antagonist. GnRH is a hormone produced in humans to regulate the release of other hormones called gonadotrophins: luteinising hormone (LH) and follicle stimulating hormone (FSH). Orgalutran blocks the action of GnRH to stop the release of gonadotrophins, especially LH.

In women, FSH is needed for growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells. LH is needed to release the mature egg cells from the follicles and ovaries (i.e. ovulation).

3. WHAT ORGALUTRAN® CONTAINS:

The active substance is ganirelix acetate.

The non-active ingredients are acetic acid, mannitol, water for injection, and sodium hydroxide.

4. WHAT ORGALUTRAN® LOOKS LIKE AND CONTENTS OF THE PACK:

Orgalutran® is available in pre-filled syringes and in packs of 1. Each pre-filled syringe contains 0.25 mg ganirelix in 0.5 ml sterile, ready to use, clear and colorless aqueous solution. Orgalutran® is to be injected under the skin (subcutaneous injection). **The needle cover contains dry natural rubber/latex which comes into contact with this product.**

5. WHEN ORGALUTRAN® SHOULD NOT BE USED:

Do not use ORGALUTRAN® if:

- you are allergic (hypersensitive) to ganirelix acetate or any other components of Orgalutran®, including dry natural rubber/latex
- you are hypersensitive to any products containing gonadotrophin releasing hormone (GnRH) or GnRH analog such as leuprolide acetate, goserelin acetate
- you have a moderate or severe kidney or liver disease
- you are pregnant

If any of these conditions apply to you, please tell your doctor before starting to use this medicine.

6. WARNINGS AND PRECAUTIONS:

Orgalutran® should be prescribed and managed by a doctor experienced in infertility treatment.

Before you use Orgalutran, tell your doctor if any of these conditions apply to you:
- if you are pregnant or breast-feeding
- if you have an allergy or any active allergic condition. Your doctor will decide, depending on the severity, if additional monitoring is required during treatment. Cases of allergic reactions have been reported as early as with the first dose.
- if you are sensitive to natural rubber latex since the packaging of Orgalutran (needle cover) contains dry natural rubber/latex which comes into contact with this product and may cause allergic reactions.
- If you are taking or have recently taken other medications including those not requiring a prescription
- if you weigh less than 50 kg or more the 90 kg

The incidence of ectopic pregnancies might be increased in women undergoing assisted reproduction. Your doctor will perform an ultrasound scan early during pregnancy to confirm that a pregnancy is intrauterine.

The incidence of congenital malformations after assisted reproduction techniques may be slightly higher than after spontaneous conceptions. This slightly higher incidence is thought to be related to characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics) and to the higher incidence of multiple gestations after assisted reproduction techniques. The incidence of congenital malformations after assisted reproduction techniques using Orgalutran is not different from that after using other GnRH analogues in the course of assisted reproduction techniques.

7. HOW TO USE ORGALUTRAN®

Always use Orgalutran® exactly as your doctor has told you. You should check with your doctor if you are not sure.

If you inject more Orgalutran than you should, contact your doctor.

In case of overdose, contact your doctor or pharmacist, emergency department of the nearest hospital, or a poison control centre immediately.

Orgalutran (0.25 mg) should be injected just under the skin once daily, as directed.

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

Daily treatment with Orgalutran should be continued for the time interval determined by your doctor. Your doctor can determine this using techniques such as ultrasound.

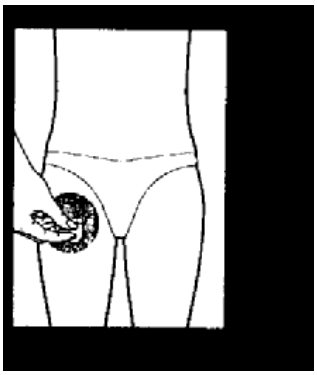
Instructions for use

Injection site
Orgalutran is supplied in pre-filled syringes and should be injected slowly, just under the skin, preferably in the upper leg.

Inspect the solution before use. Do not use if the solution contains particles or is not clear. If you administer the injections yourself or have it done by your partner, follow the instructions below carefully. Do not mix Orgalutran with any other medicines.

Preparing the injection site
Wash your hands thoroughly with soap and water.

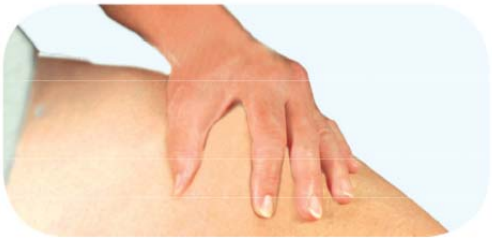
Swab the injection site with a cotton swab moistened with disinfectant (for example rubbing alcohol) to remove any surface bacteria on the skin. The most convenient site for subcutaneous injection is in the upper thigh. Clean about 5 cm (two inches) around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.



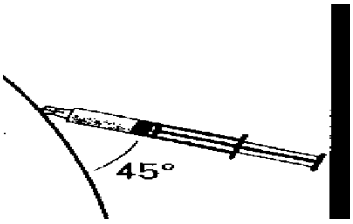
Inserting the needle

With syringe held upright, remove needle cover.

Pinch up a large area of skin between finger and thumb.

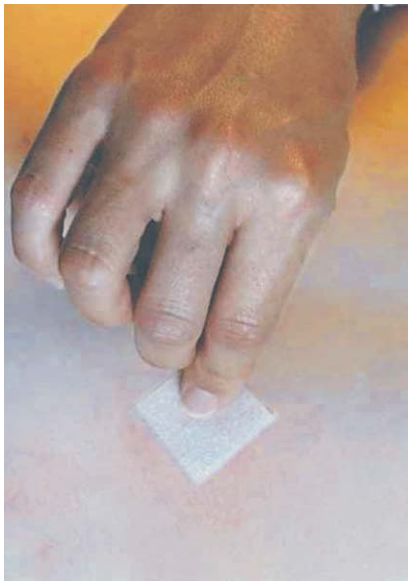


Insert the needle at the base of the pinched-up skin at an angle of 45°- 90° to the skin surface. Change the injection site with each injection.



Checking the correct needle position

Gently draw back the plunger to check if the needle is positioned correctly. Any blood drawn into the syringe means the needle tip has penetrated a blood vessel. If this happens, do not inject Orgalutran®, but remove the syringe, cover the injection site with a swab containing disinfectant and apply pressure; bleeding should stop in a minute or two.



Do not use this syringe and dispose of it properly. Start again with a new syringe.

Injecting the solution

After the needle position has been checked as described above, depress the plunger slowly and steadily, so the solution is correctly injected and the skin tissues are not damaged.

Removing the syringe

Pull the syringe out quickly and apply pressure to the site with a swab containing disinfectant (see above diagram).

Use the pre-filled syringe only once and dispose of it properly.

If you inject more Orgalutran® than you should:

Contact your doctor.

If you forget to inject Orgalutran®:

If you realize that you forgot a dose, administer it as soon as possible.
Do not inject a double dose to make up for forgotten individual doses.

If you are more than 6 hours late (so the time between two injections is longer than 30 hours) administer the dose as soon as possible, **and** contact your doctor for further advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

8. POSSIBLE SIDE EFFECTS

Like all medicines, Orgalutran® can cause side effects or reactions.

Orgalutran may cause a skin reaction such as redness, with or without swelling at the injection site. These skin reactions normally disappear within 4 hours of injection.

Very rarely, more widespread possibly allergic reactions (including various symptoms such as rash, facial swelling and dyspnea) have been observed, as early as with the first dose.

Other side effects may be headache, nausea, dizziness, asthenia (lack or loss of strength and energy) and malaise (general unwell feeling).

Additional side effects which have been known to occur with controlled ovarian hyperstimulation treatment include abdominal pain, ovarian hyperstimulation syndrome (OHSS), ectopic pregnancy (fertilized egg attaches to fallopian tube instead of the womb) and miscarriage.

During or following hormonal stimulation of the ovaries, ovarian hyperstimulation syndrome may develop. Ovarian hyperstimulation syndrome (OHSS) is a rare condition which occurs when too many follicles (part of the ovary that forms into an egg) grow and cause abdominal distension, abdominal discomfort or pain, nausea, diarrhea and sometimes difficulty in breathing. If you experience these symptoms, contact your doctor immediately as OHSS is a very serious side effect which may require treatment in the hospital.

There is one case where a patient who had eczema reported that it got worse after the

first Orgalutran dose.

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

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

9. HOW TO STORE ORGALUTRAN®

Keep out of the reach and sight of children

Do not freeze. Store at room temperature between 15°C and 30°C.

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

Do not use after the expiry date stated on the carton and on the label.

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

Contains no preservatives, therefore, each syringe is to be used only once and then properly disposed.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

PHARMACOLOGY

Ganirelix acetate is a synthetic decapeptide with high antagonistic activity against naturally occurring gonadotropin-releasing hormone (GnRH). Ganirelix acetate is derived from native GnRH with substitutions of amino acids at positions 1, 2, 3, 6, 8, and 10.

The pharmacologic effects of ganirelix acetate were evaluated in reproductive pharmacology studies in females and males and in several general pharmacology studies.

The effects of ganirelix acetate on the female reproductive endocrine system, specifically, ovulation, mating and pregnancy were evaluated in rats and dogs.

Single doses of Org 37462 (research code for ganirelix acetate), ranging from 0.125 to 2.0 mcg/rat (10 or 12 rats/group), were administered by SC injection to rats at noon of pro-oestrus. This resulted in a dose-related inhibition of ovulation with an ED_{50} of 0.29 mcg/rat which is approximately 1.4 mcg/kg. The corresponding ED_{50} value for another GnRH antagonist, detirelix, was 2.1 mcg/kg. The estrus cycle returned to normal rapidly following cessation of treatment.

A single SC dose of 3 mcg/kg Org 37462 to female rats during pro-estrus inhibited ovulation completely. Org 37462 also prevented ovulation when it was given at noon on the day before pro-oestrus as a suspension in corn oil (ED_{50} 40 mcg/kg). This anti-ovulatory effect of Org 37462 is thought to be mediated by inhibiting the pre-ovulatory surge of gonadotropins.

The effects on mating and fertility were assessed after once daily SC injections at a dose of 2.5 mcg/kg of Org 37462 in female rats. Mating of female rats to adult sexually-experienced males after at least two weeks of Org 37642 treatment (2.5 mcg/kg) resulted in a significant increase in the incidence of vaginal oestrus. There were no significant differences in mating and fertility parameters between vehicle- and Org 37462-treated females, except for a significantly lower mean number of ova and a significantly lower mean number of live pups delivered. Extending the dose to 10 mcg/kg did not alter the percentage of rats mating during treatment or 7 weeks after cessation of treatment. The fertility of mated rats, however, was significantly reduced

as shown by a decreased pregnancy rate. A significantly greater proportion of the Org 37462-treated rats mated on the first day of cohabitation; the reduction of fertility was attributed to an altered relationship between receptivity and ovulation. The effects on fertility were reversible.

Administration of Org 37462 resulted in reduced testosterone secretion in male rats, dogs and monkeys. There was a good relationship between plasma concentrations of Org 37462 and suppression of plasma testosterone levels. Org 37462 induces reversible suppression of the release of endogenous gonadotropins without initial stimulation inherent to GnRH agonists.

The effects of ganirelix acetate were investigated on histamine release and histamine-mediated effects, such as cardiovascular symptoms. Other general pharmacological properties of ganirelix were evaluated in vivo in mice, rats, dogs and monkeys. These studies included investigation of the effects of ganirelix on the central nervous, respiratory, cardiovascular, renal and digestive systems.

Org 37462 (dose range, 0.1-1000 mcg/kg SC) administered to mice, induced a small dose-related (range, 1.0-100 mcg/kg SC) increase in normal separation behaviour, miosis and a slight increase in body temperature. Org 37462 (range, 1-1000 mcg/kg SC) did not disrupt neurological or skeletal muscle co-ordination and function and did not significantly alter the onset or duration of the loss of the righting reflex induced by hexobarbital in mice. At a SC dose of 100 mcg/kg, however, the duration of action of hexobarbital was increased slightly. Org 37462 did not protect mice against a maximal electroshock induced tonic hind-limb extensor seizure, nor did it significantly affect pentylenetetrazol-induced tonic flexor and extensor seizures.

The capacity of Org 37462 to release histamine in vitro as compared to the second generation GnRH antagonist (detirelix) was assessed by means of a mixed rat peritoneal cell assay. The concentrations of antagonist that released 50% of the releasable histamine pool EC_{50} (mean ± SEM) for Org 37462 and detirelix were 17.8 ± 5.0 and 0.21 ± 0.03 mcg/mL, respectively. Thus, Org 37462 was found to be significantly less active than detirelix in this in vitro assay for histamine release.
The potential hypotensive activities of Org 37462 (range, 300-3000 mcg/kg IV) and detirelix (range, 30-300 mcg/kg IV) were studied in pentobarbital-anaesthetised rats (4 rats/group). The mean dose required to reduce mean blood pressure by 50 mmHg (ED_{50} dose and 95% confidence limits) was 901 mcg/kg (740-1140) for Org 37462 and

41 mcg/kg (22-54) for detirelix. No generalised hypersensitivity reactions in animals after SC administration have been observed. Thus, Org 37462 has less histamine releasing potential and therefore less hypotensive activity when compared to second generation GnRH antagonists.

In rats, Org 37462 (1-1000 mcg/kg SC or 0.1-100 mcg/kg IV) did not affect blood pressure or heart rate, nor did it elicit any diuretic, natriuretic or kaliuretic activity.

Org 37462 at SC doses of 1.0 and 10-100 mcg/kg (10 rats/group) increased the secretion of gastric acid and total milli-equivalents of hydrogen ions (mEq H^+) by about 50% in pylorus-ligated male rats, but the increases were not dose dependent.

Org 37462 did not induce any significant effect on respiratory rate, respiratory flow rate, tidal volume, minute volume, venous or arterial blood pO_2, pCO_2 and pH in 4 pentobarbital-anesthetized dogs, each receiving the entire dose range of 1-1000 mcg/kg SC.

SC administration of Org 37462 (range, 1-1000 mcg/kg) to 4 cynomolgus monkeys/group had no significant effect on arterial blood pressure, heart rate or behaviour.

Administration of ganirelix acetate up to 1 mg/kg SC to animals evoked no effects on the central nervous, respiratory, cardiovascular and renal systems.

Pharmacokinetics

After IV dose a $t_{½}$ was observed of 1.35 h in rats and 5 h in monkeys. This half-life is longer than one would expect of a peptide drug and inherent to the structure of ganirelix acetate. The half-life of GnRH is only a few minutes. Because of the presence of five D-amino acids ganirelix acetate is highly resistant to enzymatic degradation; it is not degraded in vitro by trypsin or chymotrypsin or by incubation with plasma. After SC administration the pharmacokinetic parameters were strongly influenced by the dosage because higher dosages resulted in depot formation at the SC injection site. The SC dose was rapidly released into the systemic circulation but as a result of depot formation t_{max} values increased with higher dosages. Absorption was probably the rate-limiting step for the systemic elimination of Ganirelix acetate. The bioavailability of ganirelix acetate after oral or nasal administration was low: < 1% relative to IV and 6% relative to SC administration, respectively.

Following a single IV dose, during the first few hours ganirelix acetate was predominantly found in tissues involved in metabolism and/or elimination. Almost all of the other organs/tissues sampled contained less than 1% of the dose at all time points.

Three metabolites, which were truncated peptides of the parent decapeptide were identified in the rat bile. Plasma and urine contained mostly undegraded ganirelix.

Whereas rat plasma did not contain metabolites, monkey plasma contained the 1-7 heptapeptide.

Excretion was mainly biliary; 13-26% and 58-84% of dosed radioactivity was recovered in urine and faeces, respectively.

TOXICOLOGY

Acute Toxicity

Dose-ranging acute toxicity studies were conducted in the rat and the cynomolgus monkey using IV and SC routes of administration. After IV administration of ganirelix acetate the approximate maximum tolerated dose was 1.0 mg/kg in rats and 3.0 mg/kg in monkeys. After SC injection of doses up to 40 mg/kg ganirelix acetate was well tolerated; no mortalities or clinical signs of systemic toxicity in the acute toxicity studies in rats and cynomolgus monkeys were observed. Local reactions at the SC injection site and pathologic changes occurred at doses $\geq$ 1 mg/kg/day with dose-related severity.

Subchronic and Chronic Toxicity

In the subchronic and chronic toxicity studies no clinical signs of systemic toxicity were present in mice, rats and monkeys at any of the dose levels tested, viz. up to 10 mg/kg SC in the 2-week toxicity studies, up to 5 mg/kg SC in the 13-week toxicity studies and up to 2.5 mg/kg SC in the 6-month chronic toxicity studies. Pharmacological effects on the reproductive organs were already observed after SC administration of 0.1 mg/kg/day (the lowest dose tested in most subchronic and chronic toxicity studies).

Reproduction and Teratogenicity

Reproductive toxicity studies in female rats showed that administration of a SC dose of 2.5 mcg/kg/day resulted in a slight decrease in fertility. SC administration of doses ≥ 100 mcg/kg/day to female or male rats for 13 weeks resulted in infertility of all treated animals. After 20 weeks of recovery, mating performance and fertility of both sexes were comparable with the vehicle-treated group, indicating reversibility of the effects on reproduction.

Exposure of a fetus to ganirelix acetate during organogenesis had no teratogenic effects. At dosages of ≥10 mcg/kg in rats and ≥30 mcg/kg in rabbits an increase in the extent of litter resorption was observed.

Carcinogenicity

Long-term toxicity studies in animals have not been performed with ganirelix to evaluate the carcinogenic potential of the drug. Ganirelix acetate did not induce a mutagenic response in the Ames test (S. typhimurium and E. coli) or produce chromosomal aberrations in *in vitro* assay using Chinese Hamster Ovary cells or mice bone marrow cells.

Mutagenicity

Ganirelix lacks genotoxic properties as demonstrated in a battery of *in vitro* and *in vivo* tests for the detection of mutagenic and clastogenic effects.

Special Toxicity

Local histamine release may cause a local reaction at the site of injection. Two sensitisation studies were performed with intradermal injections of ganirelix acetate. Overall, the response to the challenge dose of Org 37462 was comparable to the responses observed in the pre-induction and comparative-control tests. After SC administration signs of irritation were present at the injection site in ganirelix acetate-treated groups with dose-related severity and consisted of swelling and discoloration of the skin. Signs of injection-site irritation occurred occasionally in placebo-treated groups. The local tolerance outcome indicated that daily SC administered ganirelix acetate was well tolerated.

CLINICAL TRIALS

The efficacy of Orgalutran® (ganirelix acetate injection) was established in three adequate and well-controlled clinical studies. For all studies, the administration of exogenous recombinant FSH [Follistim™ (follitropin beta for injection)] 150 IU daily 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 appropriate follicular growth was achieved for administration of hCG [Pregnyl® (chorionic gonadotropin for injection)]. Following hCG administration, Orgalutran and recombinant FSH administration were discontinued. Oocyte retrieval, followed by *in vitro* fertilization (IVF) or intracytoplasmatic sperm injection (ICSI), was subsequently performed. Orgalutran has shown to be safe and effective in women undergoing multiple treatment cycles (up to a maximum of 3 cycles).

In a multicenter, double-blind, randomized, dose-finding study, the safety and efficacy of Orgalutran were evaluated for the prevention of LH surges in women undergoing COH with recombinant FSH. Orgalutran doses ranging from 62.5 mcg to 2,000 mcg and recombinant FSH were administered to 332 patients undergoing COH for IVF (see Table III). Median serum LH on the day of hCG administration decreased with increasing doses of Orgalutran. Median serum E_2 (17∃-estradiol) on the day of hCG administration was 1475, 1110, and 1160 pg/mL for the 62.5, 125, and 250 mcg doses, respectively. Lower peak serum E_2 levels of 823, 703, and 441 pg/mL were seen at higher doses of Orgalutran 500, 1,000, and 2,000 mcg, respectively. The highest pregnancy and implantation rates were achieved with the 250 mcg dose of Orgalutran as summarized in Table III.

TABLE III: **Results from the multicenter, double-blind, randomized, dose-finding study to assess the efficacy of Orgalutran® to prevent premature LH surges in women undergoing COH with recombinant FSH.**

	Daily dose (mg) of Orgalutran®					
	62.5 mcg	**125 mcg**	**250 mcg**	**500 mcg**	**1,000 mcg**	**2,000 mcg**
No. subjects receiving Orgalutran	31	66	70	69	66	30
No. subjects with ET[†]	27	61	62	54	61	27
LH rise ≥ 10 mIU/mL[*]	5	6	1	0	0	0
Serum LH (mIU/mL) on day of hCG[‡]	3.6	2.5	1.7	1.0	0.6	0.3
5th-95th percentiles	0.6-19.9	0.6-11.4	<0.25-6.4	0.4-4.7	<0.25-2.2	<0.25-0.8
Serum E_2 (pg/mL) on day of hCG[‡] 5th-95th percentiles	1475 645-3720	1110 424-3780	1160 384-3910	823 279-2720	703 284-2360	441 166-1940
No. of follicles ∃11 mm[¡§]	10.7(5.1)	10.7(4.8)	11.8(4.6)	10.1(4.7)	10.8(4.7)	10.2(5.2)
No. of oocytes[¡]	8.7(5.8)	9.6(5.4)	9.8(5.5)	8.8(6.6)	9.4(6.2)	9.1(5.3)
No. of embryos[¡]	5.2(3.6)	5.8(4.3)	5.2(4.5)	4.6(4.2)	5.5(4.4)	5.6(4.6)
No. of embryos transferred[¡]	2.7(0.9)	2.6(1.0)	2.4(0.9)	2.3(0.6)	2.4(0.8)	2.6(1.0)
Vital pregnancy rate [W]						
per attempt, n (%)	7(22.6)	17(25.8)	25(35.7)	8(11.6)	9(13.6)	2(6.7)
per transfer, n (%)	7(25.9)	17(27.9)	25(40.3)	8(14.8)	9(14.8)	2(7.4)
Implantation rate (%)[¡]	14.2(26.8)	16.3(30.5)	21.9(30.6)	9.0(23.7)	8.5(21.7)	4.9(20.1)

* Following initiation of Orgalutran therapy. Includes subjects who have complied with daily injections.
‡ Median values
§ Restricted to subjects with hCG injection
¡ Mean (standard deviation)
† ET: Embryo Transfer
W As evidenced by ultrasound at 5-6 weeks following ET.

Increases in LH ≥10 IU/L were detected in twelve subjects (62.5 mcg n=5; 125 mcg n=6; 250 mcg n=1). Transient LH rises alone were not deleterious to achieving pregnancy with Orgalutran® at doses of 125 mcg (3/6 subjects) and 250 mcg (1/1 subjects). In addition, none of the subjects with LH rises ≥10 IU/L had an associated elevation of serum progesterone above 2 ng/mL which indicates that an LH surge or premature luteinization had not occurred.

Increases in LH ≥10 IU/L prior to administration of Orgalutran on Day 6 of gonadotropin use were observed in high responders (high E_2 levels) as well as in subjects with diminished ovarian reserve (high LH and FSH levels with low E_2 levels).

Two multicenter, open-label, randomized trials were conducted to assess the efficacy and safety of Orgalutran in women undergoing COH. Follicular phase treatment with Orgalutran 250 mcg was studied using the luteal phase GnRH agonists, buserelin and leuprolide, as reference treatment in trial 38607 and 103-001, respectively. In both trials, a total of 463 and 198 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 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 are summarized in Table IV.

TABLE IV: **Results from the multicenter, open-label, randomized studies to assess the efficacy and safety of Orgalutran® in women undergoing COH.**

	Protocol 38607	Protocol 103-001
No. subjects treated	463	198
Duration of GnRH analog (days)§¥	5.4(2.0)	4.7(2.1)
Duration of recombinant FSH (days)§¥	9.6(2.0)	9.0(2.1)
Serum LH (mIU/mL) on day of hCG‡ 5th-95th percentiles	1.6 0.6-6.9	1.7 0.4-7.6
Serum E_2 (pg/mL) on day of hCG‡ 5th-95th percentiles	1190 373-3105	2001 950-4394
No. of follicles >11mm¥§	10.7(5.3)	12.3(5.8)
No. of oocytes¥	8.7(5.6)	11.67(6.7)
Fertilization rate (%)	62.1	62.4
No. subjects with ET†	399	178
No. of embryos transferred¥	2.2(0.6)	2.9(0.5)
No. of embryos¥	6.0(4.5)	6.9(4.1)
Ongoing pregnancy rate W§		
per attempt, n (%)l	94(20.3)	61(30.8)
per transfer, n (%)	93(23.3)	61(34.3)
Implantation rate (%)¥	15.7(29)	21.1(30.4)

‡ Median values
§ Restricted to subjects with hCG injection
¥ Mean (standard deviation)
† ET: Embryo Transfer
W As evidenced by ultrasound at 12-16 weeks following ET
L Includes one patient who achieved pregnancy with intrauterine induction.
Some centers were limited to the transfer of ≤ 2 embryos based on local practice standards

The mean number of days of GnRH analog treatment for subjects in the Orgalutran group was 5.4 and 4.7 days, and 2-3 weeks longer in the GnRH agonist groups in trial 38607 and 103-001, respectively. The ongoing pregnancy rate was 20.3% and 30.8% in trial 38607 and 103-001, respectively, as confirmed by ultrasound scan 12-16 weeks post embryo transfer.

Increases in LH

In trial 38607, Orgalutran® treatment, 13 subjects (2.8%) had an LH value ≥ 10 IU/L. Seven of these subjects cancelled prior to embryo transfer. The other 6 subjects had ET but did not get pregnant. For all 13 subjects Orgalutran levels were measured to check for possible compliance problems but results indicated adequate compliance.

In the buserelin group, 3 (1.3%) subjects had an LH rise during agonist treatment one

of which resulted in a cancellation. The other 2 subjects had ET and one of them got pregnant.

In trial 103-001, during Orgalutran treatment, 7 subjects (3.5%) had an LH value ∃10 IU/L. All 7 had ET, 2 had an ongoing pregnancy and 1 had a miscarriage. In the leuporelin group 1 subject (1.0%) had an LH rise during agonist treatment. This subject had ET which resulted in an ongoing pregnancy.

Some undesirable effects reported in the above trials are related to the controlled ovarian hyperstimulation treatment for ART, e.g. abdominal pain, OHSS, ectopic pregnancy and miscarriage. The overall rate of OHSS was 3.5% in the Orgalutran and 4.8% in the comparator groups.

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