ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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)[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.

Excipient with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially 'sodium-free'.

For the 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

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

In clinical studies Orgalutran was used with recombinant human follicle stimulating hormone (FSH) or corifollitropin alfa, the sustained follicle stimulant.

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 women undergoing COH. Controlled ovarian hyperstimulation with FSH or corifollitropin alfa may start at day 2 or 3 of menses. Orgalutran (0.25 mg) should be injected subcutaneously once daily, starting on day 5 or day 6 of FSH administration or on day 5 or day 6 following the administration of corifollitropin alfa. The starting day of Orgalutran is depending on the ovarian response, i.e. the number and size of growing follicles and/or the amount of circulating oestradiol. The start of Orgalutran may be delayed in absence of follicular growth, although clinical experience is based on starting Orgalutran on day 5 or day 6 of stimulation.

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).

Timing of last injection
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 hours, 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 women undergoing multiple treatment cycles.

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

Special populations

Renal impairment
There is no experience on the use of Orgalutran in subjects with renal impairment, as they were excluded from clinical studies. Therefore, the use of Orgalutran is contraindicated in patients with moderate or severe renal impairment (see section 4.3).

Hepatic impairment
There is no experience on the use of Orgalutran in subjects with hepatic impairment, as they were excluded from clinical studies. Therefore, the use of Orgalutran is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Paediatric population
There is no relevant use of Orgalutran in the paediatric population.

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 of the excipients listed in section 6.1.
- Hypersensitivity to gonadotrophin-releasing hormone (GnRH) or any other GnRH analogue.
- Moderate or severe impairment of renal or hepatic function.
- Pregnancy or breast-feeding.

4.4 Special warnings and precautions for use

Hypersensitivity reaction

Special care should be taken in women with signs and symptoms of active allergic conditions. Cases of hypersensitivity reactions (both generalised 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). 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.

Latex allergy

The needle cover contains dry natural rubber/latex which comes into contact with the needle and may cause allergic reactions (see section 6.5).

Ovarian hyperstimulation syndrome (OHSS)

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.

Ectopic pregnancy

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

Congenital malformations

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 studies investigating more than 1,000 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.

Women weighing less than 50 kg or more than 90 kg

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially ‘sodium-free’.

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 medicinal products, cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Breast-feeding

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

The use of Orgalutran is contraindicated during pregnancy and breast-feeding (see section 4.3).

Fertility

Ganirelix is used in the treatment of women undergoing controlled ovarian hyperstimulation in assisted reproduction programmes. Ganirelix is used to prevent premature LH surges that might otherwise occur in these women during the ovarian stimulation.
For posology and method of administration, see section 4.2.

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

Summary of the safety profile

The table below shows all adverse reactions in women treated with Orgalutran in clinical studies using recFSH for ovarian stimulation. The adverse reactions with Orgalutran using corifollitropin alfa for ovarian stimulation are expected to be similar.

Tabulated list of adverse reactions

The adverse reactions are classified according to MedDRA system organ class and frequency; very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). The frequency of hypersensitivity reactions (very rare, < 1/10,000) has been deduced from post-marketing surveillance.

System organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Very rare	Hypersensitivity reactions (including rash, facial swelling, dyspnoea, anaphylaxis (including anaphylactic shock), angioedema and urticaria)[1] Worsening of a pre-existing eczema[2]
Nervous system disorders	Uncommon	Headache
Gastrointestinal disorders	Uncommon	Nausea
General disorders and administration site conditions	Very common	Local skin reaction at the site of injection (predominantly redness, with or without swelling)[3]
	Uncommon	Malaise

[1] Cases have been reported, as early as with the first dose, among patients administered Orgalutran.
[2] Reported in one subject after the first Orgalutran dose.
[3] 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.

Description of selected adverse reactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, anti-gonadotrophin-releasing hormones, ATC code: H01CC01.

Mechanism of action

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.

Pharmacodynamic effects

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 0.3 - 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 cannot be excluded.
In case of a high ovarian response, either as a result of a high exposure to gonadotrophins 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 prevent these premature LH rises without compromising the clinical outcome.

Clinical efficacy and safety

In controlled studies of Orgalutran with FSH, 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. Similar

comparative studies with corifollitropin alfa using either a GnRH antagonist or long agonist protocol have not been performed.

5.2 Pharmacokinetic properties

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 body weight and serum concentrations of Orgalutran.

Absorption

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 bioavailability of Orgalutran following subcutaneous administration is approximately 91 %.

Biotransformation

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.

Elimination

The elimination half-life ($t_{½}$) is approximately 13 hours and clearance is approximately 2.4 L/h. Excretion occurs via faeces (approximately 75 %) and urine (approximately 22 %).

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

3 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 that does not contain latex. Each pre-filled syringe is affixed with a needle **closed by a needle cover of dry natural rubber/latex which comes into contact with the needle.** (See section 4.4.)

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

7. MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB 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: 10 May 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency:
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT Orgalutran 1/ 5 pre-filled syringes

1. NAME OF THE MEDICINAL PRODUCT

Orgalutran 0.25 mg/0.5 mL solution for injection
ganirelix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 0.25 mg ganirelix in 0.5 mL aqueous solution.

3. LIST OF EXCIPIENTS

Other ingredients: acetic acid, mannitol, water for injections, sodium hydroxide and acetic acid as pH adjustment.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 1 pre-filled syringe containing 0.5 mL
Solution for injection, 5 pre-filled syringes each containing 0.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.
The needle cover contains dry natural rubber/latex which comes into contact with the needle and may cause allergic reactions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/130/001 1 pre-filled syringe
EU/1/00/130/002 5 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGES TEXT Orgalutran 0.25 mg/0.5 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Orgalutran 0.25 mg/0.5 mL solution for injection
ganirelix
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Organon

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Orgalutran 0.25 mg/0.5 mL solution for injection
ganirelix

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Orgalutran is and what it is used for

Orgalutran contains the active substance ganirelix and belongs to a group of medicines called "anti-gonadotrophin-releasing hormones" which act against the actions of the natural gonadotrophin releasing hormone (GnRH). GnRH regulates the release of gonadotrophins (luteinising hormone (LH) and follicle stimulating hormone (FSH)). Gonadotrophins play an important role in human fertility and reproduction. In women, FSH is needed for the 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). Orgalutran inhibits the action of GnRH, resulting in suppression of the release of especially LH.

Orgalutran is used for

In women undergoing assisted reproduction techniques, including *in vitro* fertilisation (IVF) and other methods, occasionally ovulation may occur too early causing a significant reduction in the chance of getting pregnant. Orgalutran is used to prevent the premature LH surge that might cause such a premature release of egg cells.

In clinical studies Orgalutran was used with recombinant follicle stimulating hormone (FSH) or corifollitropin alfa, a follicle stimulant with a long duration of action.

2. What you need to know before you use Orgalutran

Do not use Orgalutran
- if you are allergic to ganirelix or any of the other ingredients of this medicine (listed in section 6);
- if you are hypersensitive to gonadotrophin releasing hormone (GnRH) or a GnRH analogue;
- if you have a moderate or severe kidney or liver disease;
- if you are pregnant or breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Orgalutran

Allergic reactions

If you have an active allergic condition, please tell your doctor. 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.

Allergic reactions, both generalised and local, including hives (urticaria), swelling of the face, lips tongue and/or throat that may cause difficulty in breathing and/or swallowing (angioedema and/or anaphylaxis) have been reported. (See also section 4.) If you have an allergic reaction, stop taking Orgalutran and seek immediate medical assistance.

Latex allergy

The needle cover contains dry natural rubber/latex which comes into contact with the needle and may cause allergic reactions.

Ovarian hyperstimulation syndrome (OHSS)

During or following hormonal stimulation of the ovaries, ovarian hyperstimulation syndrome may develop. This syndrome is related to the stimulation procedure with gonadotrophins. Please refer to the Package Leaflet of the gonadotrophin-containing medicine prescribed for you.

Multiple births or birth defects

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 woman, 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.

Pregnancy complications

There is a slightly increased risk of pregnancy outside of the uterus (an ectopic pregnancy) in women with damaged fallopian tubes.

Women weighing less than 50 kg or more than 90 kg

The efficacy and safety of Orgalutran has not been established in women weighing less than 50 kg or more than 90 kg. Ask your doctor for further information.

Children and adolescents
There is no relevant use of Orgalutran in children or adolescents.

Other medicines and Orgalutran
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility
Orgalutran should be used during controlled ovarian stimulation for assisted reproduction techniques (ART). Do not use Orgalutran during pregnancy and breast-feeding.

Ask your doctor or pharmacist for advice before taking this medicine.

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

Orgalutran contains sodium
Orgalutran contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially 'sodium-free'.

3. How to use Orgalutran

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
Orgalutran is used as part of the treatment for assisted reproduction techniques (ART) including *in vitro* fertilisation (IVF).
Ovarian stimulation with follicle stimulating hormone (FSH) or corifollitropin may start at day 2 or 3 of your period. Orgalutran (0.25 mg) should be injected just under the skin once daily, starting on day 5 or day 6 of stimulation. Based on your ovarian response, your doctor may decide to start on another day.
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.

Daily treatment with Orgalutran should be continued up to the day that sufficient follicles of adequate size are present. Final maturation of the egg cells in the follicles can be induced by administering human chorionic gonadotrophin (hCG). The time between two Orgalutran injections as well as the time between the last Orgalutran injection and hCG injection should not exceed 30 hours, as otherwise a premature ovulation (i.e. release of egg cells) 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.

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. You may notice air bubble(s) in the pre-filled syringe. This is expected, and removal of the air bubble(s) is not needed. 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 disinfectant (for example alcohol) to remove any surface bacteria. 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
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° to the skin surface. Vary 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
Once the needle has been correctly placed, 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.
Use the pre-filled syringe only once.

If you use more Orgalutran than you should
Contact your doctor.

If you forget to use Orgalutran
If you realise that you forgot a dose, administer it as soon as possible.
Do not inject a double dose to make up for a forgotten dose.
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 stop using Orgalutran
Do not stop using Orgalutran unless advised to by your doctor, as this may affect the outcome of your treatment.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The chance of having a side effect is described by the following categories:

Very common: may affect more than 1 in 10 women
- Local skin reactions at the site of injection (predominantly redness, with or without swelling). The local reaction normally disappears within 4 hours of administration.

Uncommon: may affect up to 1 in 100 women
- Headache
- Nausea
- Malaise

Very rare: may affect up to 1 in 10,000 women
- Allergic reactions have been observed, as early as with the first dose.
  - Rash
  - Facial swelling
  - Difficulty breathing (dyspnoea)
  - Swelling of face, lips, tongue, and/or throat that may cause difficulty in breathing and/or swallowing (angioedema and/or anaphylaxis)
  - Hives (urticaria)
- Worsening of a pre-existing rash (eczema) has been reported in one subject after the first Orgalutran dose.

In addition, side effects are reported which are known to occur with controlled ovarian hyperstimulation treatment (e.g. abdominal pain, ovarian hyperstimulation syndrome (OHSS), ectopic pregnancy (when the embryo develops outside the womb) and miscarriage (see the patient information leaflet of the FSH-containing preparation you are treated with)).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Orgalutran

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label after 'EXP'. The expiry date refers to the last day of that month.

Do not freeze.
Store in the original package, in order to protect from light.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Orgalutran contains
- The active substance is ganirelix (0.25 mg in 0.5 mL solution).
- The other ingredients are acetic acid, mannitol, water for injections. The pH (a measurement of the acidity) may have been adjusted with sodium hydroxide and acetic acid.

What Orgalutran looks like and contents of the pack
Orgalutran is a clear and colourless aqueous solution for injection. The solution is ready for use and intended for subcutaneous administration. **The needle cover contains dry natural rubber/latex which comes into contact with the needle.**

Orgalutran is available in packs of 1 or 5 pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Organon Belgium
Tél/Tel: 0080066550123 (+32 2 2418100)
dpoc.benelux@organon.com

България
Органон (И.А.) Б.В. - клон България
Тел.: +359 2 806 3030
dpoc.bulgaria@organon.com

Česká republika
Organon Czech Republic s.r.o.
Tel: +420 233 010 300
dpoc.czech@organon.com

Danmark
Organon Denmark ApS
Tlf: +45 4484 6800
info.denmark@organon.com

Deutschland
Organon Healthcare GmbH
Tel.: 0800 3384 726 (+49 (0) 89 2040022 10)
dpoc.germany@organon.com

Eesti
Organon Pharma B.V. Estonian RO
Tel: +372 66 61 300
dpoc.estonia@organon.com

Ελλάδα
BIANEΞ A.E.
Τηλ: +30 210 80091 11
Mailbox@vianex.gr

España
Organon Salud, S.L.
Tel: +34 91 591 12 79
organon_info@organon.com

France
Organon France
Tél: +33 (0) 1 57 77 32 00

Hrvatska
Organon Pharma d.o.o.
Tel: +385 1 638 4530
dpoc.croatia@organon.com

Ireland
Organon Pharma (Ireland) Limited
Tel: +353 15828260
medinfo.ROI@organon.com

Lietuva
Organon Pharma B.V. Lithuania atstovybė
Tel.: +370 52041693
dpoc.lithuania@organon.com

Luxembourg/Luxemburg
Organon Belgium
Tél/Tel: 0080066550123 (+32 2 2418100)
dpoc.benelux@organon.com

Magyarország
Organon Hungary Kft.
Tel.: +36 1 766 1963
dpoc.hungary@organon.com

Malta
Organon Pharma B.V., Cyprus branch
Tel: +356 2277 8116
dpoc.cyprus@organon.com

Nederland
N.V. Organon
Tel: 00800 66550123 (+32 2 2418100)
dpoc.benelux@organon.com

Norge
Organon Norway AS
Tlf: +47 24 14 56 60
info.norway@organon.com

Österreich
Organon Healthcare GmbH
Tel: +49 (0) 89 2040022 10
dpoc.austria@organon.com

Polska
Organon Polska Sp. z o.o.
Tel.: +48 22 105 50 01
organonpolska@organon.com

Portugal
Organon Portugal, Sociedade Unipessoal Lda.
Tel: +351 218705500
geral_pt@organon.com

România
Organon Biosciences S.R.L.
Tel: +40 21 527 29 90
dpoc.romania@organon.com

Slovenija
Organon Pharma B.V., Oss, podružnica Ljubljana
Tel: +386 1 300 10 80
dpoc.slovenia@organon.com

Ísland
Vistor hf.
Sími: + 354 535 7000

Italia
Organon Italia S.r.l.
Tel: +39 06 90259059
dpoc.italy@organon.com

Κύπρος
Organon Pharma B.V., Cyprus branch
Τηλ: +357 22866730
dpoc.cyprus@organon.com

Latvija
Ārvalsts komersanta "Organon Pharma B.V."
pārstāvniecība
Tel: +371 66968876
dpoc.latvia@organon.com

Slovenská republika
Organon Slovakia s. r. o.
Tel: +421 2 44 88 98 88
dpoc.slovakia@organon.com

Suomi/Finland
Organon Finland Oy
Puh/Tel: +358 (0) 29 170 3520
dpoc.finland@organon.com

Sverige
Organon Sweden AB
Tel: +46 8 502 597 00
dpoc.sweden@organon.com

United Kingdom (Northern Ireland)
Organon Pharma (UK) Limited
Tel: +44 (0) 208 159 3593
medicalinformationuk@organon.com

This leaflet was last revised in {month YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.