ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ganirelix Gedeon Richter 0.25 mg/0.5 mL solution for injection in pre-filled syringe

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 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 [N-Ac-D-Nal(2)^{1}, D-pClPhe^{2}, D-Pal(3)^{3}, D-hArg(Et2)^{6}, L-hArg(Et2)^{8}, D-Ala^{10}]-GnRH with a molecular weight of 1570.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear and colourless solution, with a pH of 4.8–5.2 and an osmolality of 260-300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ganirelix Gedeon Richter 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 ganirelix was used with recombinant human follicle stimulating hormone (FSH) or corifollitropin alfa, the sustained follicle stimulant.

4.2 Posology and method of administration

Ganirelix Gedeon Richter should only be prescribed by a specialist experienced in the treatment of infertility.

Posology

Ganirelix 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. Ganirelix Gedeon Richter (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 ganirelix 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 ganirelix may be delayed in absence of follicular growth, although clinical experience is based on starting ganirelix on day 5 or day 6 of stimulation.

Ganirelix and FSH should be administered approximately at the same time. However, these medicinal products 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 ganirelix 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 gonadotropin (hCG).

Timing of last injection

Because of the half-life of ganirelix, the time between two injections of ganirelix as well as the time between the last injection of ganirelix and the hCG injection should not exceed 30 hours, as otherwise a premature LH surge may occur. Therefore, when injecting ganirelix in the morning, treatment with ganirelix should be continued throughout the gonadotropin treatment period including the day of triggering ovulation. When injecting ganirelix in the afternoon the last injection of ganirelix should be given in the afternoon prior to the day of triggering ovulation.

Ganirelix has shown to be safe and effective in women undergoing multiple treatment cycles.

The need for luteal phase support in cycles using ganirelix 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 ganirelix in subjects with renal impairment, as they were excluded from clinical studies. Therefore, the use of ganirelix is contraindicated in patients with moderate or severe renal impairment (see section 4.3).

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

Paediatric population
There is no relevant use of Ganirelix Gedeon Richter in the paediatric population.

Method of administration

Ganirelix Gedeon Richter 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 Ganirelix Gedeon Richter themselves, provided that they are adequately instructed and have access to expert advice.

For instructions of the medicinal product before administration, see section 6.6 and the instructions for use included at the end of the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to gonadotropin-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 ganirelix, 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, ganirelix should be discontinued and appropriate treatment administered. In the absence of clinical experience, ganirelix treatment is not advised in women with severe allergic

conditions.

Ovarian hyperstimulation syndrome (OHSS)

OHSS may occur during or following ovarian stimulation. OHSS must be considered an intrinsic risk of gonadotropin 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 new-borns it has been demonstrated that the incidence of congenital malformations in children born after COH treatment using ganirelix 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 ganirelix have not been established in women weighing less than 50 kg or more than 90 kg (see also sections 5.1 and 5.2).

Excipient

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 Ganirelix Gedeon Richter 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 ganirelix in clinical studies using recFSH for ovarian stimulation. The adverse reactions with ganirelix 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 ganirelix.
[2] Reported in one subject after the first ganirelix 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 ganirelix-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 also 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 ganirelix in humans are available. Clinical studies with subcutaneous administration of ganirelix 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, ganirelix treatment should be (temporarily) discontinued.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Ganirelix is a GnRH antagonist, which modulates the hypothalamic-pituitary-gonadal axis by competitive binding to the GnRH receptors in the pituitary gland. As result a rapid, profound, reversible suppression of endogenous gonadotropins occurs, without initial stimulation as induced by GnRH agonists. Following administration of multiple doses of 0.25 mg ganirelix 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 ganirelix treatment was 5 days. During ganirelix 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 gonadotropins 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 ganirelix treatment on day 5 can prevent these premature LH rises without compromising the clinical outcome.

Clinical efficacy and safety

In controlled studies of ganirelix with FSH, using a long protocol of GnRH agonist as a reference, treatment with the ganirelix 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 ganirelix (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 ganirelix.

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 ganirelix 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 ganirelix 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

Non-clinical 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

Glacial acetic acid
Mannitol (E 421)
Water for injections
Sodium hydroxide (for pH-adjustment)

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

The medicinal product is filled in a glass syringe with staked stainless steel needle, closed with a plunger stopper and supplied with a plunger rod. The injection needle is provided with a rigid needle shield.

Pack sizes of 1 pre-filled syringe or 6 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each pre-filled syringe is intended for only one injection.

Alcohol swabs, gauze pads and sharps container are needed for administration of this medicinal product but are not provided in the pack.

Precautions to be taken before handling or administering the medicinal product

The syringe should be inspected before use. Use only syringes with clear, particle-free solutions and from undamaged containers.
Before using this medicinal product for the first time, the patient should carefully read the instructions for use at the end of the package leaflet where instructions are provided on how to administer Ganirelix Gedeon Richter.

Air bubble(s) may be seen in the pre-filled syringe. This is expected, and removal of the air bubble(s) is not needed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The used syringes need to be disposed of in a sharp disposal container.

7. MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1658/001
EU/1/22/1658/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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 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 manufacturer responsible for batch release

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

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

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ganirelix Gedeon Richter 0.25 mg/0.5 mL solution for injection in pre-filled syringe
ganirelix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid, mannitol (E 421), water for injections, sodium hydroxide as pH adjustment.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe
6 pre-filled syringes

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.

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

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1658/001 [1 pre-filled syringe]
EU/1/22/1658/002 [6 pre-filled syringes]

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ganirelix Gedeon Richter

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

LABEL

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

Ganirelix Gedeon Richter 0.25 mg/0.5 mL injection
ganirelix

SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ganirelix Gedeon Richter 0.25 mg/0.5 mL solution for injection in pre-filled syringe
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 Ganirelix Gedeon Richter is and what it is used for

Ganirelix Gedeon Richter contains the active substance ganirelix and belongs to a group of medicines called "antigonadotropin-releasing hormones" which act against the actions of the natural gonadotropin-releasing hormone (GnRH). GnRH regulates the release of gonadotropins (luteinising hormone (LH) and follicle stimulating hormone (FSH)). Gonadotropins 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). Ganirelix Gedeon Richter inhibits the action of GnRH, resulting in suppression of the release of especially LH.

Ganirelix Gedeon Richter 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. Ganirelix Gedeon Richter is used to prevent the premature LH surge that might cause such a premature release of egg cells.
In clinical studies ganirelix 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 Ganirelix Gedeon Richter

Do not use Ganirelix Gedeon Richter
- if you are allergic to ganirelix or any of the other ingredients of this medicine (listed in section 6);
- if you are hypersensitive to gonadotropin-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 Ganirelix Gedeon Richter.

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 using Ganirelix Gedeon Richter and seek immediate medical assistance.

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 gonadotropins. Please refer to the package leaflet of the gonadotropin-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 ganirelix 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 ganirelix 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 Ganirelix Gedeon Richter in children or adolescents.

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

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

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

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

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

3. How to use Ganirelix Gedeon Richter

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Ganirelix Gedeon Richter 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. Ganirelix Gedeon Richter (0.25 mg) should be injected into the fatty layer 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.

Ganirelix Gedeon Richter and FSH should be administered approximately at the same time. However, these medicines should not be mixed and different injection sites are to be used.

Daily treatment with Ganirelix Gedeon Richter 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 gonadotropin (hCG).
The time between two injections of Ganirelix Gedeon Richter as well as the time between the last injection of Ganirelix Gedeon Richter and hCG injection should not exceed 30 hours, as otherwise a premature ovulation (i.e. release of egg cells) may occur.
Therefore, when injecting Ganirelix Gedeon Richter in the morning treatment with Ganirelix Gedeon Richter should be continued throughout the gonadotropin treatment period including the day of triggering ovulation.
When injecting Ganirelix Gedeon Richter in the afternoon the last injection of Ganirelix Gedeon Richter should be given in the afternoon prior to the day of triggering ovulation.

Instructions for use
Before the administration of this medicine it is very important that you also carefully read and closely follow the detailed instructions for use provided at the end of this package leaflet.

Injection site
Ganirelix Gedeon Richter is supplied in pre-filled syringes and should be injected slowly, into the fatty layer 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 and at the end of the Package leaflet carefully. Do not mix Ganirelix Gedeon Richter 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 shield. Pinch a fold of skin between index 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 Ganirelix Gedeon Richter, 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, push the plunger down slowly and steadily, so the solution is correctly injected and the skin tissues are not damaged. Push the plunger down until the syringe is empty and wait for 5 seconds.

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 Ganirelix Gedeon Richter than you should
Contact your doctor.

If you forget to use Ganirelix Gedeon Richter
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 Ganirelix Gedeon Richter
Do not stop using Ganirelix Gedeon Richter 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
– Feeling generally unwell (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 ganirelix 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 package 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 possible 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 Ganirelix Gedeon Richter

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 label and on the carton 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.

Each pre-filled syringe is only for a single use of injection.

Alcohol swabs, gauze pads and sharps container are needed for administration of this medicine but they are not provided in the pack.

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 Ganirelix Gedeon Richter contains
- The active substance is ganirelix (0.25 mg in 0.5 mL solution).
- The other ingredients are: glacial acetic acid, mannitol (E 421), water for injection. The pH (measurement of the acidity) may have been adjusted with sodium hydroxide (see section 2 “Ganirelix Gedeon Richter contains sodium”).

What Ganirelix Gedeon Richter looks like and contents of the pack
Ganirelix Gedeon Richter is a clear and colourless solution for injection (injection). The medicine is filled in a glass syringe with staked stainless steel needle, closed with a plunger stopper and supplied with a plunger rod. The injection needle is provided with a rigid needle shield.

Ganirelix Gedeon Richter is available in packs of 1 pre-filled syringe or 6 pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

This leaflet was last revised in

Other sources of information

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

Instructions for use

HOW TO PREPARE AND ADMINISTER GANIRELIX GEDEON RICHTER IN PRE-FILLED SYRINGE

Before the administration of this medicine, carefully read these instructions and the package leaflet the whole way through.

These instructions will help you with how to give yourself or how your partner can give you an injection of Ganirelix Gedeon Richter. If you are not sure about administering the injection or you have any questions, please ask your doctor or pharmacist for help.
Do not mix Ganirelix Gedeon Richter with any other medicines.
Perform the injection at the same time each day.
Each pre-filled syringe contains one daily dose of ganirelix.

CONTENTS OF THE INSTRUCTIONS FOR USE

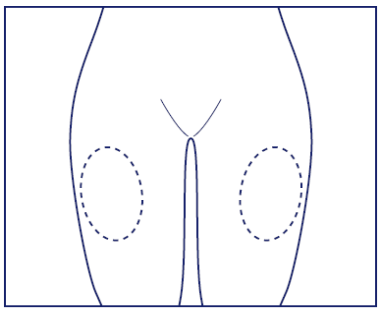
1. Preparing for the injection

- Wash your hands thoroughly with soap and water. It is important that your hands and the items you use are as clean as possible to avoid infections.
- Find a clean area for the items you need for the injection, e.g. a clean table or similar horizontal surface.
- Gather everything you need and lay them out into the clean area:
  - Swabs containing disinfectant (e.g. alcohol)
  - 1 pre-filled syringe containing the medicine
    - Do not hold the syringe by the plunger to avoid syringe disassembling.
    - Do not use this medicine after the expiry date which is stated on the label or on the carton after EXP. The expiry date refers to the last day of that month.
  - A puncture-resistant container (e.g. a plastic bottle with a wide enough opening) to dispose the used syringe safely.
- Inspect the solution before use.
- You may notice air bubble(s) in the pre-filled syringe. This is expected, and removal of the air bubble(s) is not needed.
- Do not use the syringe if:
  - it is cracked or damaged, or
  - the needle shield has been removed or is not tightly attached or
  - a fluid leakage is visible or
  - the solution looks abnormal (it contains particles or it is not colourless).

  If any of these occurs, you should dispose the syringe safely into the sharps container and use another one.

2. Preparing the injection site

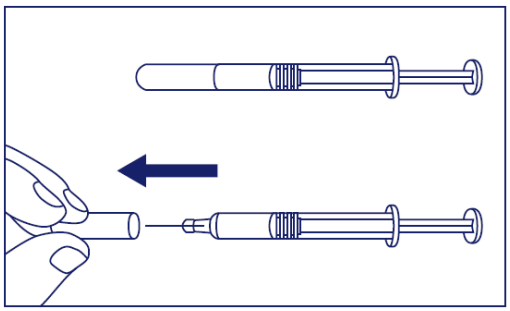
- Choose the injection site preferably in the upper leg. The injection site should be varied for each injection to prevent the damage of tissue under the skin.



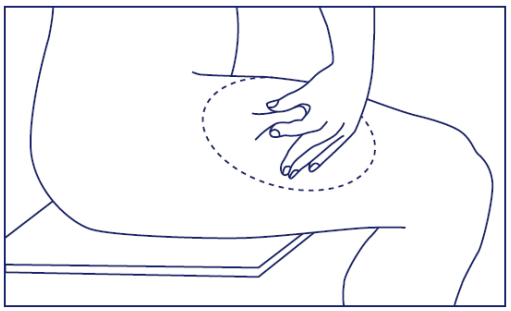
- Do not inject yourself in any area that is tender, damaged or bruised. Always choose an intact skin area for injecting the medicine.
- Do not inject through clothes.
- Administer Ganirelix Gedeon Richter and follicle stimulating hormone (FSH) approximately at the same time. However, these medicines should not be mixed, and different injection sites are to be used.
- Swab the injection site with a disinfectant (for example alcohol) at the chosen injection site to remove any surface bacteria. Clean an area of about 5 cm (two inches) in diameter around the point where the needle will go in and let the disinfectant dry for about 1 minute before proceeding.
- Do not touch the injection site again or blow on it before the injection.

3. Injecting the medicine

- You receive Ganirelix Gedeon Richter in pre-filled syringes with a staked needle, ready for administration without any further adjustments to the syringe.
- By grabbing the middle of the syringe body, remove 1 syringe from the pack.
- For injecting the medicine, pull off the needle shield from the syringe that is held horizontally and pointing away from you. Do not twist but pull the needle shield off.

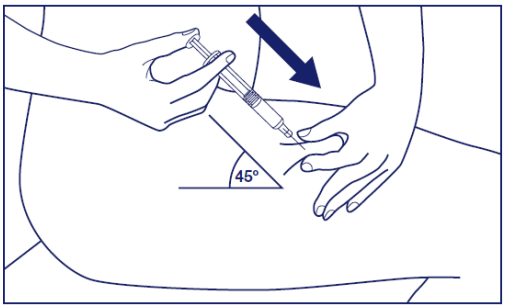


- When handling the syringe, do not touch the syringe tip or the needle with your fingers to avoid contamination.
- At the chosen and disinfected injection site, pinch up a fold of skin between your index finger and thumb.



- Administer Ganirelix Gedeon Richter subcutaneously, i.e. into the fatty layer just under the skin.
- Hold the syringe with your other hand so that you can place your thumb onto the plunger when

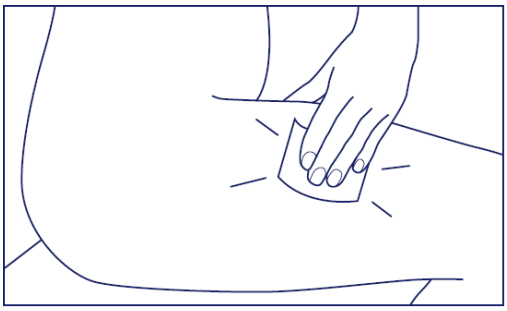
needed. Insert the needle completely with a quick, firm action into the middle of the pinched-up skin at an angle of 45° to the skin surface.



- 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 Ganirelix Gedeon Richter, 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 and use a new syringe.
- Once the needle has been correctly placed, push the plunger down with your thumb slowly and steadily, so the solution is correctly injected and the skin tissues are not damaged.
- Push the plunger down until the syringe is empty.

4. After the injection

- Wait for 5 seconds (slowly count to 5), then let go of the skin you are pinching.
- Pull the syringe out quickly from your skin and apply pressure to the site with a swab containing disinfectant.



- Do not rub your skin after the injection.
- Use each pre-filled syringe only once.
- Do not recap the needle to avoid needle stick injury.
- Discard the used syringe safely in the puncture-resistant container immediately, and return to the pharmacy for a correct disposal. Ask your pharmacist how to dispose of medicines you no longer use.