SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fyremadel 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 (as acetate) in 0.5 ml aqueous solution. The active substance ganirelix (as acetate) (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
Sodium.
Each pre-filled syringe contains <1 mmol sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear and colourless aqueous solution with a pH between 4.5 to 5.5 and an osmolality between 250 to 350 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ganirelix 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 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 (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, 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 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 gonadotrophin (hCG).

Timing of last injection
Because of the half-life of ganirelix, the time between two ganirelix injections as well as the time between the last ganirelix injection 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 gonadotrophin treatment period including the day of triggering ovulation. When injecting ganirelix in the afternoon the last ganirelix injection 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 in the paediatric population.

Method of administration
Ganirelix 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 themselves, provided that they are adequately instructed and have access to expert advice.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients 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 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.

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 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 section 5.1 and 5.2).

This medicine 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 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 (≥1/1000 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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-gonadotrophin 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 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 ganirelix to female volunteers serum LH, FSH and E2 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 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 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

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, glacial (E260)
Mannitol (E421)
Water for injection
The pH may have been adjusted with sodium hydroxide and acetic acid, glacial.

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pre-filled syringes made of colourless type I glass containing 0.5 ml of sterile, ready for use, aqueous solution closed with the grey rubber plunger stopper and polypropylene plunger rod. Injection needles (27 G) affixed to the barrel and provided with grey elastomeric needle shield and polypropylene rigid needle shield. Each pre-filled syringe is affixed with a needle covered with a needle cover containing dry natural rubber/latex which comes into contact with the needle.

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

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Polarisavenue 87

2132 JH Hoofddorp

The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 31750/0055

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/08/2018

10 DATE OF REVISION OF THE TEXT

14/04/2020