SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Orgalutran. This scientific discussion has been updated until 1 May 2002. For information on changes after this date please refer to module 8B.

1. Introduction

Ganirelix is the active substance for the medicinal product Orgalutran. Ganirelix is a synthetic decapeptide that possesses competitive antagonistic activity to gonadotropin-releasing hormone (GnRH, gonadorelin, LHRH) and reversibly inhibits the secretion of pituitary gonadotropins, thereby preventing a surge in luteinising (LH) hormone, which would negatively affect the fertilisation rate by premature ovulation.

Current practice in controlled ovarian hyperstimulation (COH) combines stimulation by exogenous gonadotropins with the suppression of endogenous gonadotropins by GnRH agonists. Use of agonists gives rise to an initial flare-up of endogenous gonadotropin secretion and therefore requires a 2-3-week pre-treatment to achieve complete suppression.

Orgalutran is indicated for the prevention of premature luteinising hormone (LH) surges in women undergoing COH for assisted reproduction techniques (ART). In clinical trials Orgalutran was used with recombinant human follicle stimulating hormone (FSH).

Controlled ovarian hyperstimulation with FSH may start at day 2 or 3 of menses. Orgalutran (0.25 mg) should be injected subcutaneously once daily, starting preferably on day 6 FSH administration. The start of Orgalutran may be delayed in absence of follicular growth, although clinical experience is based on starting Orgalutran on day 6. Daily treatment with Orgalutran should be continued up to the day that sufficient follicles of adequate size are present. Because of the half-life of ganirelix, the time between two Orgalutran injections and between the last Orgalutran injection and the hCG injection should not exceed 30 hrs, as otherwise a premature LH surge may occur.

Orgalutran is formulated as sterile, ready for use solution for subcutaneous injection, as a prefilled syringe containing 0.25 mg ganirelix (as free base) per 0.5 ml.

2. Chemical, pharmaceutical and biological aspects

Composition

Composition: Orgalutran is presented as sterile, ready for use solution for subcutaneous injection in a prefilled syringe containing 0.25 mg ganirelix (as free base) per 0.5 ml. The excipients included are mannitol, acetic acid, sodium hydroxide and/or acetic acid (pH adjustment) and water for injections.

Containers: Ready-for-use, 1 ml disposable syringe of colourless borosilicate glass (hydrolytic glass type I). The syringe is provided with a stainless steel needle and a natural rubber needle shield and closed by a siliconised, grey rubber piston. The disposable pre-filled glass syringe is for single use only.

Active substance

Ganirelix is a synthetic decapeptide. The proposed specifications for the active substance are acceptable, but will be re-evaluated, when more experience is gained.

Batch analysis data are provided for nine lots. These are in accordance with proposed specifications.

Based on the stability results obtained, it is recommended to store the ganirelix drug substance at a temperature of 2-8°C in closed amber class bottles with a re-test date of 2 years. Furthermore, during transport and for short-term storage during production, the drug substance can be stored at 25°C for 1 month. In addition the drug substance should be protected from high relatively humidity, using closed

bottles, to prevent moisture uptake. Long-term exposure of the unprotected drug substance to day light should be avoided.

Other ingredients

All ingredients are of Ph. Eur and USP/NF quality where relevant.

Product development and finished product

Clinical trial formula

A total of 10 batches have been used in the clinical program and ganirelix concentration was in the range of 0.125 mg/ml to 4.0 mg/ml. Otherwise the composition of batches is essentially the same as that for the marketed product. In contrast to the marketed product, all clinical batches were filled in 2-ml vials (0.5 ml extractable volume per vial).

Development pharmaceutics

A range of ganirelix formulations from 0.125 to 10 mg/ml was tested under stress conditions (oxygen, nitrogen, air, sterilisation and variable pH) and the optimal characteristics of the formulation and the manufacturing process were defined. The formulations, 0.125 and 4.0 mg/ml were also tested in a compatibility study with packaging materials.

Manufacturing process and process validation

The manufacturing process is adequately described and all the steps of the process validation are regarded as standard operation procedures. The process was validated with respect to homogeneity of the bulk solution, filtration, filling and terminal sterilisation.

Specifications of the medicinal product

The controls on the finished product are comprehensive and include pharmaceutical tests (colour, clarity, pH, relative osmotic pressure, extractable volume, sterility and particles) and are performed using standard compendial methods. A reversed phase HPLC is used for identification and assay of ganirelix and determination of degradation products. HPTLC identification of ganirelix is used at release. The LAL test was used for the determination of bacterial endotoxins (Ph.Eur). The proposed specifications for the finished product are acceptable, but will be re-evaluated, when more experience is gained.

Batch analysis results

Analysis data of six batches of Orgalutran 0.5 mg/ml solution for injection are provided. The results show that the proposed specifications are fulfilled.

Stability of the medicinal product

Stability data on three batches of 18-month storage at 5°C, 25°C/60% RH, 30°C/60% RH and of 6-month storage at 40°C/75% RH are provided. The finished product is sensitive to light; therefore the product should be protected from light during storage.

Shelf life: Based on the stability data, a shelf life of 18 months is acceptable when the product is stored in the original package in order to protect from light. The product cannot be frozen. New stability data were submitted to extend the shelf life from 18 months to 2 years on 28 June 2001. The section 6.3 of the SPC was updated accordingly (positive CPMP opinion on 16 July 2001).

Discussion on Chemical and pharmaceutical and biological aspects

The quality of this product is considered acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way**.**

Remaining points are indicated to be addressed post-approval.

3. Toxico-pharmacological aspects

Pharmacodynamics

Synthetic analogues of GnRH with a deletion or substitution of the histidine in position 2 have been shown to be competitive antagonists of the native hormone. Ganirelix has a 9-fold higher receptor binding affinity (K_d = 0.4 nM) as compared to GnRH (K_d = 3.6 nM). No clinically relevant receptor binding was found among 62 general receptor binding assays. It has also been demonstrated that ganirelix inhibits GnRH-induced LH and FSH release from rat pituitary cells in a concentration-dependent manner.

The anti-gonadotropic potency of ganirelix was investigated in female and male animals. Ganirelix treatment of female rats resulted in a dose-related inhibition of ovulation with an ED_{50} of 0.3 µg/rat (1.4 µg/kg) when administered at noon on pro-oestrus. Ganirelix treatment at 2.5 µg/kg/day resulted in an increase in the incidence of vaginal oestrus. Treatment with 2.5 or 10 µg/kg/day did not affect mating but fertility was slightly reduced. During treatment with much higher dosages (0.7 and 5.0 mg/kg/day) a reversible complete blocking of the oestrus cycle and mating occurred. After cessation of treatment circulating level dropped below 1 ng/ml and fertility returned to normal.

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

General Pharmacology programme

The general pharmacology profile of ganirelix has been investigated in a number of standard experimental procedures and in addition in studies aiming to elucidate histamine-releasing properties of ganirelix using rat peritoneal cell assay.

Central nervous system

In general gross behaviour studies in mice a small dose-related increase in CNS stimulation (abnormal separation of mice) was found. Ganirelix did not modify maximal electroshock-induced tonic seizures or pentylenetetrazole-induced seizures in mice. Furthermore ganirelix did not have any effect on the ability of mice to remain on the wire (neurological deficit test). In contrast, there was a significant increase in duration of the loss of righting reflex induced by hexobarbital at 0.1 mg/kg s.c. of ganirelix. In addition, ganirelix had a slight hyperthermic effect (at 0.1 mg/kg, s.c., but not with the higher dose). Hence the latter two effects may have been a chance finding since neither were observed at the higher dose.

Cardiovascular system

All investigated GnRH antagonists including ganirelix induced marked blood pressure reduction in rats following intravenous administration. However, there is a 600-fold safety margin to the antiovulatory effect (antiovulatory action: ED_{50} 1.4 µg/kg s.c.; hypotensive activity: ED_{50} 900 µg/kg i.v.). Ganirelix does not change blood pressure or heart rate at doses up to 1 mg/kg s.c. or 0.1 mg/kg iv. in rats. Ganirelix did not change arterial blood pressure, heart rate or behaviour in cynomolgus monkeys at doses up to 1 mg/kg given s.c.

Respiratory system

Ganirelix did not change (up to 1 mg/kg s.c.) any respiration related parameters in dogs.

Renal effects

Ganirelix did not have any significant diuretic, natriuretic or kaliuretic effects at doses up to 1 mg/kg sc.

Gastrointestinal effects

Ganirelix at s.c. doses of 0.001 and 0.01-0.1 mg/kg was reported to increase the secretion of gastric acid by about 50% in pylorus-ligated male rats. However, the increase in gastric acid secretion was not dose-related and is therefore unlikely to be directly associated with administration of ganirelix.

Effects of ganirelix on histamine release *in vitro*:

Histamine releasing properties of ganirelix and detirelix (another GnRH antagonist) were investigated in rat peritoneal cells. The EC_{50} was 17.8 µg/ml for ganirelix and 0.2 µg/ml for detirelix. This low histamine releasing potency of ganirelix is in line with its mild hypotensive effect.

Pharmacokinetics

Pharmacokinetics of ganirelix was tested in a number of species using single dose administration mainly of ^{3}H-labeled ganirelix. At 1 mg/kg i.v. plasma $t_{½}$ was about 1.4 h in rats and 5 h in monkeys. After s.c. administration, the elimination mainly depends on liberation of ganirelix from the injection depot, at least at larger doses used in experimental animals. Ganirelix is rapidly distributed to all tissues, with the highest amounts of radioactivity found in the liver and the small intestine. Very low levels were present in the bone, brain, eye, fat, muscle, pituitary and thyroid. Protein binding in vitro was 82-84 % in human, monkey and rat plasma. Excretion of ganirelix was mainly biliary, since 58-84 % of the dosed radioactivity was found in faeces and only 13-26 % in urine (rats and monkeys). Three truncated metabolites were identified in bile. Binding of these metabolites to the human GnRH receptor was about 100 fold lower in comparison to the parent compound ganirelix. The pharmacokinetics of ganirelix after single and repeated doses has been sufficiently investigated.

Toxicology

Single dose toxicity

Single dose toxicity studies were performed in rats and monkeys. Ganirelix administered s.c. up to 40 mg/kg induced no mortality in both species. Predominant effects were atrophy/ weight reduction of the reproductive organs and skin irritation at the injection site.

Repeated dose toxicity

Repeated dose toxicity studies were conducted in mice, rats, cynomolgus monkeys and rabbits. Data have been provided to demonstrate that the ganirelix exposure of different animal species used in toxicology studies was sufficient as compared to man.

In general, ganirelix was well tolerated. Effects on reproductive organs were seen in many studies, which is in agreement with the known pharmacological action of ganirelix. In mice, subchronic ganirelix caused ovarian interstitial cell hyperplasia in all investigated doses (1,3 and 10 mg/kg/day s.c. for three months). Toxic effects were also in spleen and liver, like hemosiderosis and hepatocytic midzonal hypertrophy. In rats, decreased erythrocyte counts were observed, as well increased levels of AST and ALT at the highest ganirelix dose (10 mg/kg/day s.c.). In many cases some degree of local irritation and inflammation at the injection site were observed.

Reproduction studies

In female rats, fertility was impaired at a subcutaneous dose beyond 0.5 µg/kg/day. In a 13-week repeated dose toxicity study, male rats proved infertile at doses of 0.1 µg/kg/day and higher. Ganirelix administered during pregnancy/organogenesis resulted in a significant increase of the number of resorptions in rats receiving 10 µg/kg/day and rabbits receiving 30 or 50 µg/kg/day. Teratogenic effects were not observed in foetuses from ganirelix treated dams.

Mutagenic potential

Ganirelix was not mutagenic in Salmonella typhimurium or in Escherichia coli. Furthermore, ganirelix did not induce chromosome aberrations or mutations in mammalian cells with or without S9-mix and was also negative in the i*n vivo* bone marrow micronucleus test was performed in male and female mice. All mutagenicity and genotoxicity studies conform to Good Laboratory Practice.

Carcinogenicity potential

No formal carcinogenicity studies have been conducted based on the short duration of the treatment, ie. from 5 to maximally 14 days, which is acceptable. Although women may undergo multiple treatment cycles, the treatment is never aimed to be continuous

Local tolerance

Ganirelix has no sensitising potential in the guinea pig assay performed.

Special toxicity studies

Ganirelix is compatible with human blood.

Discussion on toxico-pharmacological aspects

Ganirelix is a GnRH antagonist with high receptor binding affinity (K_d = 0.4 nM). Ganirelix treatment of female rats resulted in a dose-related inhibition of ovulation with an ED_{50} of 1.4 µg/kg when administered at noon on pro-oestrus. Ganirelix treatment at 2.5 µg/kg/day resulted in an increase in the incidence of vaginal oestrus. Treatment with 2.5 or 10 µg/kg/day did not affect mating but fertility was slightly reduced. During treatment with much higher dosages (0.7 and 5.0 mg/kg/day) a reversible complete blocking of the oestrus cycle and mating occurred. After cessation of treatment fertility returns to normal. Ganirelix has mild histamine releasing potential. Generalised hypersensitivity reactions after s.c. Administration has not been observed. Administration of ganirelix up to 1 mg/kg s.c. to animals evoked no effects on the central nervous, respiratory, cardiovascular and renal systems. Ganirelix did not induce any unexpected toxic effects. Ganirelix exposure of different animal species used in toxicology studies was sufficient as compared to man. The predominant effects observed in mice, rats and monkeys relate to the pharmacodynamic action of the drug.

4. Clinical aspects

Ganirelix is a competitive antagonist to gonadotropin-releasing hormone (GnRH, gonadorelin, LHRH) and it reversibly inhibits the secretion of pituitary gonadotropins.

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

In clinical trials Orgalutran was used with recombinant human follicle stimulating hormone (FSH).

Controlled ovarian hyperstimulation with FSH may start at day 2 or 3 of menses. Orgalutran (0.25 mg) should be injected subcutaneously once daily, starting on day 6 FSH administration. The start of Orgalutran may be delayed in the absence of follicular growth, although clinical experience is based on starting Orgalutran on day 6. Daily treatment with Orgalutran should be continued up to the day that sufficient follicles of adequate size are present. Because of the half-life of ganirelix, the time between two Orgalutran injections and between the last Orgalutran injection and the hCG injection should not exceed 30 hrs, as otherwise a premature LH surge may occur.

The pharmacodynamic and pharmacokinetic properties of ganirelix were investigated in altogether five phase I/II trials. Documentation of efficacy was based on the results of three pivotal, multicenter, randomised, controlled studies (38607, 38616 and 103-001) and a phase II dose finding study (38602). In addition, pregnancy and delivery follow-up was presented for the subjects who got pregnant in these trials.

Clinical pharmacology

The pharmacodynamic and pharmacokinetic properties of ganirelix were investigated in both healthy volunteers and women receiving IVF in five phase I/II trials. The studies were conducted in compliance with GCP.

Overview of trials presenting pharmacokinetic and/or pharmacodynamic data is given in the table below:

Protocol	Trial description	No. of subjects*	Dose (mg)	Route
Single dose trials				
38604	Single-centre, open-label, randomised, two-way cross-over trial to assess absolute bioavailability	19	0.25	IV SC
38613	Single-centre, open-label trial to assess the excretion balance and metabolite Profile	3	1	IV
Multi-dose trials				
38605	Single-centre, open-label, randomised, parallel-design trial to assess dose-proportionality and pharmacokinetics	15 15 15	0.125 0.25 0.5	SC
38612	Single-centre, open-label, randomised, two-way cross-over trial to assess local tolerance and bioavailability **	16	2.0	SC
38602	Multi-centre, randomised, double-blind dose-finding trial to determine the optimal dose of Org 37462 in IVF subjects	31 66 70 69 66 30	0.0625 0.125 0.25 0.5 1.0 2.0	SC

* All subjects treated with Org 37462

Pharmacodynamics

The prevention of premature LH surges is achieved through competitive binding of ganirelix to the GnRH receptors in the pituitary gland. As a result of this binding suppression of (1) Luteinising Hormone (LH), (2) Follicle Stimulating Hormone (FSH) occurs. The ganirelix suppression of the release of LH and FSH may affect also (3) Estradiol (E2) levels.

In young female volunteers, after administration of 0.125, 0.25 and 0.5 mg, a sustained and consistent suppression of LH was only observed at 0.5 mg/day of ganirelix at 24 hours after the preceding injection. However, a dose-dependent, but variable suppression was observed at 4-6 hours after the last of seven injections. The pre-dose serum LH levels increased during the study and a further increase (mild rebound) was observed after the last injection. Similar patterns were observed for FSH and E2. The median time to return of menses was 30 days (min 12, max 38 days), after the last injection.

A much higher than recommended dose (2 mg/day for 14 days) of ganirelix provided a profound suppression of serum LH, FSH and E2 in healthy women. Progesterone concentrations were only slightly affected.

In the phase I-II studies in healthy women and subjects scheduled for IVF, the effect of ganirelix on serum LH and FSH appears to fade within a few days after initial clear suppression. The same phenomenon is observed in men in whom cyclic changes in gonadotropins are not a complicating factor.

Pharmacokinetics

The mean absolute bioavailability of ganirelix following a single s.c. dose (0.25 mg) was 91% (Study 38604). The volume of distribution approximates to total body water. After s.c. injection, t_{max} was 0.75-1.5 h. Serum concentrations in all subjects were above the lower limit of quantification (0.02 ng/ml) until at least 24 hours from the s.c. injection.

Following multiple doses of ganirelix (0.125, 0.25 or 0.5 mg s.c.) given once daily steady state was observed between days 2 and 3 (Study 38605). No statistically significant dose-effect was found for

the dose-normalised parameters C_{max} and $C_{ss,\ min}$, indicating dose proportionality. No statistically significant difference between the dose groups was found for the parameters t_{max}, t_{ss}, DF and weight-normalised Cl_{app}. The dose normalised AUC_{0-24} of the 0.25 mg dose group was statistically significantly higher compared to the 0.125 mg and 0.5 mg dose groups. The differences, however, were not remarkable and are probably without clinical significance. A statistically significant difference was found between $t_{½}$ in the lowest dose group and the other two dose groups. At the proposed dose of 0.25 mg/day, $t_{½}$ was approximately 16 hours.

Pharmacokinetic analysis indicates an inverse relationship between bodyweight and serum concentrations of ganirelix. 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. The applicant addressed this issue at the oral explanation to the CPMP and these findings are addressed in the Summary of Product Characteristics.

The excretion balance and metabolite profile was studied following a single intravenous injection of [^{14}C]-labeled ganirelix in healthy female volunteers of reproductive age (Study 38613). Approximately 90% of the dose was excreted in urine and faeces within 192 hours. Over the entire collection period (up to 768 h), 22.1% of the dose was recovered in urine and 75.1% in faeces. Urinary excretion was completed within 24 h after drug administration, whereas faecal excretion was almost completed within 192 hours. An apparent elimination half-life of 10.4 h was found for plasma [^{14}C]-radioactivity.

Unchanged ganirelix was the major radioactive compound present in plasma up to 4 h postdose (50-70%). Additional compounds included the 1-7 peptide (10-15% of radioactivity). Unchanged ganirelix was also the main compound in urine but was not observed in faeces. The 1-4 and 1-6 peptides were not observed in human plasma, but only in urine and faeces.

Interaction studies

No specific pharmacokinetic and/or pharmacodynamic interaction studies were performed.

Since ganirelix is degraded by hydrolysis, the potential for pharmacokinetic interactions is deemed to be low. The lack of interaction studies and that the possibility of interactions with commonly used medicinal product including histamine liberating products can not be excluded are indicated in the SPC (see Section 4.5 of the SPC Interaction with other medicinal product and other forms of interaction).

Special groups

Pharmacokinetics in special subgroups like patients with renal or hepatic impairment, elderly and children were not investigated. In view of the proposed indication, this is acceptable. However, the use of Orgalutran in patients with moderate to severe liver or renal impairment is contraindicated (see section 4.3 of the SPC Contraindications).

Pregnancy and lactation

No clinical data on exposed pregnancies are available. It is not known whether ganirelix is excreted in breast milk. The use of Orgalutran is contraindicated during pregnancy and lactation (see Section 4.3 of the SPC Contraindications and section 4.6 of the SPC Pregnancy and Lactation).

Clinical efficacy

The efficacy claim is based on the results of three pivotal, multicentre, randomised, controlled studies (38607, 38616, 103-001) and a phase II dose finding study (38602). In addition, pregnancy and delivery follow-up was presented. The total number of subjects who received ganirelix in the phase II and III studies (excluding the follow-up studies) is 1386. The different study design characteristics are described below.

Type of study	Studies No	Design	N*	Route / Duration	Dose
Dose finding Phase II	38602	MC, DB, R, MD Healthy females of infertile couples	31 66 70 69 66 30	s.c. , starting at day 6 of ovarian stimulation, once daily for a maximal duration of 14 days.	0.0625 mg 0.125 mg 0.25 mg 0.50 mg 1 mg 2 mg
Therapeutic confirmatory Phase III	38607	MC,O,R, MD, P, using buserelin (B) as a reference treatment including healthy females of infertile couples	463 238	G:s.c., starting at day 6 of ovarian stimulation once daily for a maximal duration of 14 days. B: intranasally four times daily starting 2 to 4 weeks prior to ovarian stimulation.	0.25mg (G) 0.6mg (B)
	38616	MC, O, R, MD, Using triptorelin (T) as a reference treatment including healthy females of infertile couples	226 111	G: s.c, once a day, starting on day 6 of ovarian stimulation for a maximal duration of 14 days T: s.c once daily starting 2 to 4 weeks prior to ovarian stimulation.	G: 0.25 mg T:0.1 mg
	103-001	MC, O, R, MD, Using leuprolide (L) as a reference treatment including healthy females of infertile couples	198 99	G: s.c, once daily, starting on day 6 of ovarian stimulation for a maximal duration of 14 days L: s.c, once daily starting 2 to 4 weeks prior to ovarian stimulation.	G:0.25 mg L: 1.0 mg

* All-Subjects-Treated group

As described below the primary efficacy variable in the phase III study was the mean number of oocytes and the ongoing pregnancy rate. In the analysis of phase II study, per protocol amendment, a distinction between primary and secondary efficacy variables was not made.

The need for luteal phase support in cycles using Orgalutran has not been studied. In clinical trials, luteal phase support was given according to study centres' practice. Major exclusion criteria in the trials included endocrine abnormality, abnormal cervical smear, current type I hypersensitivity, epilepsy, diabetes, cardiovascular, gastrointestinal, renal or pulmonary disease, most of which were usual exclusion criteria for ART.

The clinical efficacy and safety studies were conducted according to GCP.

Dose-response studies and main clinical studies

Dose response studies

Protocol 38602 is a phase II, multi-center, double-blind, randomised, dose-finding study to select the minimal effective dose of ganirelix to prevent premature LH surges. The study was conducted in 13 study centres, in nine countries.

Once daily, one of six doses of GnRH antagonist ganirelix (0.0625 mg, 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg) was administered subcutaneously (sc) in women undergoing COH for IVF. For COH, recFSH treatment with fixed dose (150 IU) was to start on day 2 of the menstrual cycle by one daily sc injection, preferentially in the upper leg or arm. On day 6 of FSH treatment, ganirelix treatment was started by daily sc injections, at the same time the dose of recombinant FSH (recFSH) was adjusted depending on the ovarian response as assessed by daily ultrasound. Urinary hCG was injected for ovulation induction when there were at least 3 follicles $\geq$ 17 mm observed. Oocyte pick-up was performed 30 to 36 hours thereafter, followed by in vitro fertilisation/ intra cytoplasmic sperm injection (IVF/ICSI). Luteal support was given as intravaginal/intramuscular progesterone or HCG.

Results

In total, 342 women were randomised of whom 332 received ganirelix. 58.4% of the women had primary infertility. The number of subjects treated with 0.0625 mg and 2 mg of ganirelix was lower than the other treatment groups, as randomisation to these groups was stopped prematurely, following the advice of the External Independent Advisory Committee. The lowest dose group was stopped because of a too high incidence of LH rises and the highest dose group because of poor clinical outcome (ovarian response).

The serum LH and rises of estradiol (E2) decreased with increasing ganirelix doses. Serum FSH levels were similar between dose groups.

The total amount of recFSH administered was not different between the dose groups, and the median daily recFSH dose ranged between 150 IU and 183 IU. The total duration of ovarian stimulation with recFSH was 10 days. On the day of HCG, the number of follicles $\geq$ 11 mm were similar in all the six dose groups, whereas serum E2 levels were highest in the lowest ganirelix group, i.e. 1475 pg/ml and lowest in the highest ganirelix group, i.e. 430 pg/ml. The mean number of oocytes and embryos was similar in all groups. The implantation rate and pregnancy rate per attempt was lowest in the 2 mg group (1.5 % and 3.8% respectively) and highest in the 0.25 mg group (21.9% and 36.8 % respectively).

A daily dose of 0.25 mg of ganirelix prevented premature LH rises in 98.6% (68/69) women undergoing COH (one patient is not included due to lack of compliance). The dose-finding study shows that daily dose of 0.25 mg should be optimal based on preventing premature LH surges and clinical outcome (number of oocytes and good quality embryos, implantation rate and vital pregnancy rate). However, the optimal starting day of ganirelix during COH has not been studied prospectively, e.g. according to follicle size as assessed by ultrasound. Also, in this study only patients with normal LH/FSH ratio and normal BMI range have been included. In clinical IVF programs, many patients have either subnormal or elevated LH levels. The applicant was asked to clarify this issue at an oral explanation. The CPMP concluded that there are very limited data (8 subjects) which suggest, that in subjects with normal FSH, but elevated LH (day 1 and/or day 6 of stimulation), ganirelix suppresses LH levels.

Main studies

Protocol 38607 is a phase III, multi-center, open-label, randomised (ratio 2:1) study to assess the efficacy and safety of ganirelix in women undergoing COH for IVF/ICSI, using a long protocol of buserelin as a reference treatment. The study was conducted in 20 centres, in 10 countries. The total number of subjects in the Intent-to-Treat group was 701 (463 subjects in ganirelix group and 238 subjects in the buserelin group).

The trial was designed to show non-inferiority of ganirelix to buserelin. For the number of oocytes, a non-inferiority margin was choosen and the applicant compared the one-sided confidence interval for the difference between ganirelix and control groups to that margin. However, instead of defining a delta and using one-sided confidence intervals, the applicant compared for pregnancy rates the point estimate of the difference between ganirelix and control groups to a predefined margin. This practice is not in accordance with current guidance.

The selected ganirelix dose, 0.25 mg was administered once daily sc, starting at day 6 of ovarian stimulation. The reference treatment was buserelin, 0.6 mg daily, intranasally, (0.15 mg four times a day). If down-regulation had not occurred after 14 days, the dose was doubled. Both ganirelix and buserelin were continued during recFSH treatment, until hCG injection. Because the COH treatment

regimens for agonist and antagonists are dissimilar, i.e. agonist treatment starting two to four weeks prior to ovarian stimulation and antagonist treatment starting after five days of FSH stimulation, it was impossible to conduct a blinded trial.

Primary efficacy variables were the number of cumulus-oocyte-complexes and ongoing pregnancy rate. Secondary efficacy variables were treatment failure and number of good quality embryos. The study was designed to show that the combination of efficacy, safety and convenience of ganirelix is not clinically inferior to the current care, i.e. GnRHa treatment in a long protocol. For the ongoing pregnancy rate per attempt a treatment difference within a margin of -5% was considered to be acceptable taking into account an expected ongoing pregnancy rate of about 22%. For cumulus-oocyte-complexes the margin was -3 oocytes.

Results

On day 6 of recFSH treatment, just prior to the first ganirelix injection, 20 subjects (4.3%) had an LH value > 10 IU/l, the E2 values in these subjects ranged from 348 to 1900 pg/ml. For 15 of the 20 subjects with an LH rise, LH levels were measured again after two ganirelix injections and for 14 out of these 15 subjects, LH had decreased to below 10 IU/l.

The incidence of LH rises >10 IU/l during ganirelix and COH treatment was 2.8% and seemed to be unfavourable for the clinical outcome. Also, in order to prevent premature LH rises, daily compliance was considered to be essential.

The comparison of LH levels between the two treatment groups up to two weeks after ET indicates a more rapid recovery from pituitary suppression in the ganirelix group.

The mean number of cumulus-oocyte-complexes per attempt was 8.7 in the ganirelix group and 9.7 in the buserelin group, the difference was within the specified non-inferiority margin. However, the ongoing pregnancy rates per attempt were 20.3% in the ganirelix group and 25.7% in the buserelin group, the difference being 5.4% (97.5% lower confidence limit -11.9%), outside the specified non-inferiority margin.

The median duration of ganirelix treatment was five days, and that of buserelin treatment 26 days. The median duration of recFSH treatment was 9 days in the ganirelix group and 10 days in the buserelin group, the total recFSH doses administered were 1500 IU and 1800 IU, respectively. In the ganirelix group, 13 subjects (2.8%) showed rises of serum LH > 10 IU/l (all of them were checked for compliance, and none of them got pregnant), in the buserelin group 3 subjects (1.3%). Median serum E2 on the day of or on the day before hCG was 1190 pg/ml and 1700 pg/ml for the ganirelix and buserelin groups, respectively. The mean fertilisation rate was equal in both groups (62.1%). The implantation rate was 15.7% in the ganirelix group and 21.8% in the buserelin group, resulting in the vital pregnancy rates per attempt of 21.8% and 28.2%, respectively.

The ongoing pregnancy rates differed between the study centres. In view of the different pattern of follicular growth and the lower oestradiol levels per antral follicle on the day of hCG administration in the ganirelix group, it is considered important that recFSH dose adjustments are based primarily on the number and size of the follicles and not on the levels of circulating oestradiol. This information has been included in the Summary of Product Characteristics.

Trial 103-001 (ganirelix vs. leuprorelin)

This was a Phase III, multicenter, open-label, randomised study of healthy female partners of infertile couples scheduled for in vitro fertilisation (IVF). Patients were allocated either to the Orgalutran (0.25 mg/day s.c. in the upper leg, 1-14 days) treatment group or to the leuprolide acetate (1.0 mg/day for a maximum of 21 days) reference group. Progesterone was to be administered to subjects for luteal support according to the routine standard care for the investigator's site.

In the ganirelix group, recFSH treatment was to begin on the second or third day of the menstrual cycle (starting dose 225 IU for the first five days, thereafter adjusted according to ultrasoud scan findings). Ganirelix treatment was to begin on day 6 of recFSH treatment. hCG was administered when an adequate ovarian response was observed (at least 3 follicles ≥ 17 mm). In the leuprolide group, recFSH treatment was to begin after adequate suppression with leuprolide was achieved. A higher starting dose of recFSH was used in this study compared study 38607 (150 IU/day).

A total of 313 subjects were randomised (208 in the Orgalutran group and 105 in the leuprorelin acetate group).

Primary efficacy variables identified were the number of oocytes retrieved and ongoing pregnancy rate. The study treatment failure and number of good quality embryos obtained were the secondary efficacy variables.

The ongoing pregnancy rate per attempt was 30.8% in the ganirelix group and 36.4% in the leuprorelin group (lower one-sided 97.5% confidence limit for estimated treatment difference -15.7%).

The mean number of oocytes was 11.6 in the ganirelix group and 14.1 in the leuprorelin group (lower one-sided 97.5% confidence limit for estimated treatment difference –4.0), which exceeded the pre-set non-inferiority margin of -3.

During ganirelix treatment, 3.5 % (n=7) subjects had a LH value > 10 IU/l compared to only one subject in the leuprorelin group.

Trial 38616 (ganirelix vs. triptorelin)

This was a multi-center, open-label randomised (2:1) trial comparing the efficacy and safety of ganirelix with a long protocol of GnRH agonist triptorelin.

In total, 355 subjects were randomised, 236 to Orgalutran and 119 to triptorelin. Of these subjects, 337 received treatment (all according to randomisation), 226 women received Orgalutran, and 111 received triptorelin.

Ganirelix (0.25 mg/day) was administered once daily per s.c. injection (in the upper leg), starting at day 6 of ovarian stimulation. The minimum duration of treatment was 1 day and maximum 14 days. Triptorelin was given once daily per s.c. injection of 0.1 mg in the upper leg. If down-regulation had not occurred after 14 days, treatment with triptorelin was extended with a maximum of two times one week. After down-regulation, recFSH treatment was started. During recFSH Treatment Day 1 through 5, the daily dose of recFSH was to be fixed to 150 IU. Triptorelin administration continued during ovarian stimulation, with a maximum of another 19 days. Luteal phase support: progesterone was to be given daily, starting at the latest at the day of embryo transfer (ET), for 2 weeks, or up to menses. If pregnancy occurred, luteal phase support could be continued for several additional weeks.

Primary efficacy variables were the number of oocytes and ongoing pregnancy rate.

The treatment failure rate (treatment failure defined as a subject not having an hCG injection, or the hCG injection given because of premature luteinisation) in the ITT population was 4.9% in the ganirelix group and 4.5% in the triptorelin group.

The mean number of oocytes per attempt in the ITT group was 7.9 in the ganirelix group and 9.6 in the triptorelin group. The estimated treatment difference, based on adjusted-for-center means (7.3 and 8.6, respectively) was -1.3 oocyte, with a lower one-sided 97.5% confidence limit of -2.4 oocyte. This difference is within the non-inferiority margin.

The mean number of good quality embryos in the ITT group was 2.7 embryos in the ganirelix group and 2.9 embryos in the triptorelin group. The estimated treatment difference, based on adjusted-for-center means (2.2 and 2.5, respectively) was -0.3 embryo.

The ongoing pregnancy rates per attempt in the ITT group (including two spontaneous pregnancies in the triptorelin group) were 31.0% in the ganirelix group and 35.1% in the triptorelin group. The estimated treatment difference, based on adjusted-for-center pregnancy rates of ganirelix and triptorelin (31.3% and 35.1%, respectively), was -3.8%. The ongoing pregnancy rates per attempt for the ITT group minus the subjects who were found spontaneously pregnant during down regulation with triptorelin, were 31.0% in the Org 37462 group and 33.9% in the triptorelin group. The estimated treatment difference, based on adjusted-for-center pregnancy rates of 31.4% and 33.9%, respectively, was -2.5%.

Supportive studies

Experience on repeated cycles

Study 38608 was a single-centre, open-label trial designed to assess the safety of ganirelix (0.25 mg/day) in women undergoing 1, 2 or 3 controlled ovarian hyperstimulation (COH) cycles and possible several frozen embryo cycles (prior to the third treatment cycle), and scheduled for IVF with or without ICSI. A total of 167 women received treatment.

Seventy-nine subjects (47%) continued with a second cycle and 30 out of 79 received ganirelix during a third cycle. In total, 47 subjects had at least one frozen embryo cycle.

The mean number of oocytes for the ITT group was 7.4, 5.1 and 5.8 for cycles 1, 2 and 3, respectively. Mean implantation rates were rather low, but comparable between cycles. Ongoing pregnancy rates per attempt were similar between treatment cycles for the ITT group, i.e. 17.3%, 16.5% and 16.7% for cycle 1, 2 and 3, respectively. When frozen embryo cycles were included, the ongoing pregnancy rates were 20,8%, 16.5% and 16.7%, respectively (cumulative rate 31.5%).

The frequency of adverse events, including local injection site reactions was similar during the first and subsequent treatment cycles. No antibody formation was detected.

Discussion on the clinical efficacy

The proposed dose of ganirelix was appropriately chosen on the basis of a phase II dose-ranging trial and dose related safety.

The pivotal phase III trials failed to demonstrate non-inferiority according to the ICH guidelines for ongoing pregnancy rate compared with long GnRH agonist regimens. In all three trials there was a tendency towards a lower pregnancy rate with ganirelix. Overall, the pregnancy rate in the three phase III trials was 25.4% in the ganirelix group and 30.1% in the GnRH agonist groups. In all three pivotal phase III trials a smaller number of oocytes was obtained in the ganirelix regimen compared with long GnRH agonist regimens. Overall, combined analysis showed a treatment difference of –1.3 oocytes, with a lower 97.5% confidence limit of –1.9 oocytes.

The observed differences for pregnancy rate and oocytes were considered clinically acceptable.

Overall, the incidence of LH rises (≥ 10 IU/L) was slightly higher during ganirelix treatment (2.4%). Considering LH rises along with concomitant progesterone rises (≥ 1 ng/mL), the incidence was comparable to GnRH agonist regimens (1.2% versus 0.8%).

Given the rapid reversibility of the effect of ganirelix, compliance with recommended posology is obviously an important factor for efficacy of the medicinal product.

Clinical safety
Patient exposure

The Integrated Summary of Safety (ISS) includes 22 trials at the cut-off day of August 31, 1998. However, 11 of these trials have limited value for the assessment of safety of ganirelix in the proposed indication, as a number of studies were performed in men and higher than recommended doses and treatment durations were used. The applicant submitted further safety information from studies, which were ongoing at the time of the MAA submission, including pregnancy follow-up and reports of repeated use and two additional comparative phase III trials. Overall in the 4 controlled efficacy and safety trials (38602, 38607, 38616 and 103-001), 1217 women have been treated with ganirelix. In addition, 167 women received ganirelix in the open phase III study 38608.

Adverse events (AE) and serious adverse event/deaths

No subjects died in any of the clinical pharmacology trials. There were no maternal deaths in any of the efficacy and safety trials, including pregnancy and delivery follow-up studies.

Overall, in the 4 controlled clinical trials (38602, 38607, 38616 and 103-001) the incidences of adverse events (AEs) and serious adverse events (SAEs) were 23.1% and 3.0% respectively. The most frequent SAEs were ectopic pregnancy, miscarrige and OHSS; well known complications of ART.

There were no important differences in the frequency of ectopic pregnancies and miscarriage between ganirelix and comparators.

Common AEs (≥1%) in the ganirelix treatment groups were headache, abdominal pain (gynaecological), foetal death, ovarian hyperstimulation syndrome (OHSS), vaginal bleeding, abdominal pain (gastrointestinal), nausea and injection site reaction. Injection site reactions were generally observed during the first 4 hours following injection.

Uncommon AEs (< 1%) were dizziness, asthenia and malaise. Most of the AEs in the clinical trials were rated as mild or moderate, only 1.6% were rated as severe.

The overall safety profile of ganirelix in the controlled clinical trials were generally similar to GnRH agonist treatment. However, a lower incidence of injection site reactions was observed for ganirelix than for GnRH agonists. One hour after injection, the incidence of at least once a moderate or severe local skin reaction per treatment cycle was 12% in ganirelix treated patients and 25% in patients treated subcutaneously with a GnRH agonist.

Worsening of pre-existing eczema has been reported in one subject after first ganirelix dose.

Importantly, no SAEs attributable to generalised histamine release have been reported.

The most serious complication of COH is OHSS. In the 4 main trials the overall incidence of OHSS was 2.9% in the ganirelix groups and 3.8% in the comparator groups. A high incidence of OHSS was observed in study 103-001, which could be related to the high dose of FSH used.

One subject in clinical pharmacology trial 38605 became pregnant after ganirelix treatment before the first spontaneous menses. After six months of pregnancy, the subject delivered a dead baby with hydrocephalus and a cleft palate. A trisomy was found. The date of conception is reported to have been 7 days after the last 0.125 mg dose of ganirelix. The event was judged unlikely related to study drug by both the investigator and the sponsor. However, a causal role cannot be excluded completely.

A great majority (95%) of subjects (n=74) in the clinical pharmacology studies experienced at least one AE. All AEs were rated mild or moderate. The most frequent treatment-related AEs were headache, injection site reaction, hot flushes, dizziness and fatigue. Most of these AEs may partly be ascribed to the down-regulation of FSH and LH and therefore may occur less during IVF treatment due to the exogenous administration of FSH.

Discontinuations

Discontinuations due to AEs were rare in the controlled trials (0-0.4%) and not more frequent during ganirelix treatment than during GnRH agonist treatment. The reported reasons for discontinuation were risk of developing OHSS.

One subject in the clinical pharmacology studies discontinued due to worsening of existing eczema after the first ganirelix injection. Injection was not given to the affected skin area.

Laboratory findings

There were no obvious differences in the proportion of subjects with at least one post-baseline clinically significant abnormal haematology value between the ganirelix and the GnRH agonist groups. Clinically significant abnormal biochemistry values were observed in more than 1% of subjects for low blood glucose, low Pi, high Pi and high total bilirubin. However, the incidences were similar in both ganirelix and GnRH agonist groups.

Abnormal low or high systolic or diastolic blood pressure values (or clinically significant decrease or increase from baseline) were infrequent in both ganirelix and buserelin groups. There were no apparent differences between the groups. Relative increase from baseline in body weight of at least 7% was observed in 1.3% and 3.5% of subjects in the ganirelix and buserelin groups, respectively.

Pregnancy and children follow-up

In total, 339 women who had an ongoing pregnancy after treatment with ganirelix participated in 5 follow-up trials. Of these, 159 fully completed the follow-up study, as per the cut-off date of the Consolidated Response, and for these completed subjects all safety data on both mother and infants is available. The total number of infants born from completed subjects is 197. All infants were optionally

followed up to maximally 8 weeks after birth. At the time of submission of the MAA, of the 73 live-born infants, SAEs were reported in 7 (9.6%), AEs in 15 (20.5%) and AEs of severe intensity in 3 infants (4.1%). The SAEs were foetal maturation impaired (n=2), neonatal sepsis, neonatal apnoea and arrhythmia, premature birth (twin pregnancy), exomphalos/tongue disorder (autosomal dominant Beckwith Wiedemann syndrome). In addition, one case of trisomy 18 was diagnosed after the delivery of a still-born foetus. Other foetal disorders (reported as "minor") were clubfoot (n=1), skull malformation (1), naevus (1), pyloric stenosis (1), and skin malformation (1). Neonatal jaundice was reported in three infants (4.1%) and polycythemia in one infant. No cases of infants with abnormal psychomotor development were reported.

Compared to the GnRH agonist regimens, a slightly higher incidence of total anomalies (major and minor) were reported following ganirelix treatment. The applicant was requested to provide and update based on ongoing follow-up studies at an oral explanation to the CPMP.

Based on the clinical data and a review of literature concerning the incidence of congenital anomalies in the general population and in the context of ART, the CPMP concluded that currently there is no evidence of increased incidence of major anomalies. The data as regards to minor anomalies are inconclusive.

The applicant agreed to provide additional data on pregnancy and children follow-up as stated in the letter of undetaking dated 19 January 2000 (see also section on Post-marketing experience).

Discussion on clinical safety

Based on the data obtained, ganirelix has an acceptable safety profile. Ganirelix is a weak histamine liberator. Only local reactions associated with this property have been reported so far, however, the possibility of a generalised reaction cannot be excluded, especially in subjects with concomitant allergic symptoms. Therefore, appropriate warnings were included in the Summary of Product Characteristics. Short-lived injection site reactions are frequent. Altogether, discontinuations due to adverse events were rare in the phase II and III studies.

The overall safety profile of ganirelix is similar to GnRH agonists in the three phase III trials. A slightly lower incidence of injection site reactions in observed for ganirelix than for comparators. The incidence of OHSS, an important complication of COH, is similar with ganirelix and GnRH agonist regimens.

Altogether, the current data do not indicate an increased risk of congenital anomalies following treatment with ganirelix compared to long GnRH-agonist regimens or to published incidence figures.

The applicant agreed to provide additional data on pregnancy and children follow-up as stated in the letter of undertaking dated 19 January 2000 (see also section on Post-marketing experience).

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Preclinical pharmacology and toxicology
Ganirelix is a GnRH antagonist with high receptor binding affinity (K_d = 0.4 nM). Ganirelix treatment of female rats resulted in a dose related inhibition of ovulation.

Ganirelix has mild histamine releasing potential. Generalised hypersensitivity reactions after s.c. Administration has not been observed.

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

Ganirelix did not induce any unexpected toxic effects. Ganirelix exposure of different animal species used in toxicology studies was sufficient as compared to man. The predominant effects observed in mice, rats and monkeys relate to the pharmacodynamic action of the drug.

Efficacy

The proposed dose of ganirelix was appropriately chosen on the basis of a phase II dose-ranging trial and dose related safety. At a dose of 0.25 mg/day s.c, sufficient suppresion of LH secretion is produced in view of the therapeutic indication.

Phase III trials indicated a tendency towards a lower ongoing pregnancy rate and less oocytes with the ganirelix regimen compared with long GnRH agonist regimens. However, these observed differences are considered clinically acceptable in view of the overall risk/benefit of the product.

Overall, the incidence of LH rises was low during ganirelix treatment and the incidence of LH rises along with concomitant progesterone rises was comparable to the incidence in the GnRH agonist regimens.

Safety

Based on the data obtained, ganirelix has an acceptable safety profile. Short-lived injection site reactions are frequent, but generally occurred less often than after GnRH agonist injections. Altogether, discontinuations due to adverse events were rare in the phase II and III studies.

The incidence of OHSS during ganirelix treatment, an important complication of COH, was similar to that reported for GnRH agonists. The overall safety profile of ganirelix is similar to comparators in the three phase III trials.

The current data do not indicate an increased risk of congenital anomalies following treatment with ganirelix compared to long GnRH-agonist regimens or to published incidence figures. However, the applicant has been asked to provide additional data on pregnancies after Orgalutran treatment with a focus on infant outcome in the indicated timeframe as agreed in the letter of undertaking dated 19 January 2000 (see also section on Post-marketing experience).

Benefit/risk assessment

During an oral explanation held during the CPMP on 14 December 1999, the applicant addressed the following issues: the overall benefit/risk profile of ganirelix compared to GnRH agonists, the effect of body weight on the pharmacokinetics of ganirelix and finally the company's proposal for follow-up/monitoring of congenital anomalies (pregnancy, delivery and infant outcome).

Phase III trials indicated a tendency towards a lower ongoing pregnancy rate and less oocytes with the ganirelix regimen compared with long GnRH agonist regimens. However, these observed differences are considered clinically acceptable in view of the overall risk/benefit of the product.

Overall, the incidence of LH rises was low during ganirelix treatment and the incidence of LH rises along with concomitant progesterone rises was comparable to the incidence in the GnRH agonist regimens.

Based on the data obtained, ganirelix has an acceptable safety profile. The current data do not indicate an increased risk of congenital anomalies following treatment with ganirelix compared to long GnRH-agonist regimens or to published incidence figures. However, the applicant has been asked to provide additional data on pregnancies after Orgalutran treatment with a focus on infant outcome in the indicated timeframe as agreed in the letter of undertaking dated 19 January 2000 (see also section on Post-marketing experience).

Based on the CPMP review of available data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Orgalutran in the prevention of premature luteinising hormone surges in women undergoing controlled ovarian hyperstimulation for assisted reproduction techniques was favourable.

6. Post-marketing experience

Follow-up data on pregnancy outcome from the current clinical trial programme - As follow-up measure, the Marketing Authorisation Holder provided the analysis of the updated clinical trials database, which suggests the following:

The total incidence of congenital malformations is slightly higher in the ganirelix group compared to GnRH agonist treatment groups (7.6% vs. 5.5%). The Odds Ratio is 1.4 (95% CI 0.65-3.0). However, the incidence of all malformations is within the reported incidence of 6-10% according to the CDER/CBER reviewer guidance for "Evaluation of human pregnancy outcome data" (June 1999).

The incidence of major congenital malformations is slightly higher in the ganirelix group compared to GnRH agonist group regardless of whether a conventional definition (1.4% vs. 0.6%) or a broader definition (4.1% vs. 3.3%) is used. The Odds Ratio is 2.5 (95% CI 0.3-20.5). However, the incidence figures are within or below those reported in literature (2-4%).

The update does not suggest any specific pattern in the reported malformations.

Overall, the data presented do not imply that ganirelix increases the incidences of anomalies in newborns. The continuation of follow-up studies is recommended.