RISK MANAGEMENT PLAN (RMP)

Ganirelix

Solution for injection

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Kenilworth, New Jersey, USA

Version: 2.0

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[redacted]

Risk Management Plan Template Approval Date: 12 APR 2010

EXECUTIVE SUMMARY

Ganirelix is a Gonadotropin Releasing Hormone (GnRH) antagonist which has been developed for the prevention of premature Luteinising Hormone (LH) surges during Controlled Ovarian Stimulation (COS) for Assisted Reproductive Technology (ART). Ganirelix has been approved by European Medicines Agency (EMEA) on 17 May 2000 via the Centralised Procedure. This update to the first issue of the Risk Management Plan (RMP) for ganirelix has been prepared as requested by the CHMP in the Rapporteur's Assessment Report for European Risk Management Plan v 1.0. There are no safety issues, extension of dosage form, and/or extension of indication that urged the submission of this RMP.

Ganirelix comes as a solution for injection in a prefilled syringe (0.25 mg/ 0.5 mL). Ganirelix should be injected subcutaneously once daily. The posology included in the current EU labeling text describes that ganirelix treatment is to be started on Day 6 of ovarian stimulation and may be delayed in the absence of follicular growth. Meanwhile, new data have become available that additionally support an earlier start of ganirelix treatment, meaning that treatment can be initiated on Day 5 or Day 6 of ovarian stimulation, depending on the ovarian response. Daily treatment should be continued up to the day that sufficient follicles of adequate size are present.

Initially, COS combined stimulation by exogenous gonadotropins with GnRH agonist treatment to achieve pituitary suppression in order to control endogenous gonadotropin synthesis and release. Use of GnRH agonists, however, gives rise to an initial flare-up of endogenous gonadotropin secretion and requires a 2- to 3-week pretreatment period to achieve complete suppression. In contrast, GnRH antagonists immediately (within only a few hours) suppress endogenous gonadotropin secretion without initial stimulation and therefore require administration during only a short period of the stimulation, namely when a premature LH surge is likely to occur.

Common reported drug-related adverse events are administration site reactions (12%). Nausea was reported in 0.5%, headache in 0.4%, and malaise in 0.3% of the patients. Very rarely cases of hypersensitivity reactions including various symptoms such as rash, facial swelling, and dyspnea have been reported among patients administered ganirelix with follicle stimulating hormone (FSH). Other reported undesirable effects are related to the COS treatment for ART, notably pelvic pain, abdominal distension, OHSS, ectopic pregnancy, and spontaneous abortion. Evaluation of all safety data and possible risk factors related to ganirelix, revealed hypersensitivity and injection site reactions as important identified risks.

ART-related events reviewed in this plan are OHSS, congenital malformations, multiple pregnancy, spontaneous abortion, ectopic pregnancy, ovarian torsion, thromboembolic events and malignant neoplasm. These effects are not related to ganirelix but to the target population undergoing ART treatment and/or to the ART treatment and the resulting pregnancy. There is important missing information about

the use of ganirelix in patients with renal or hepatic impairment, pregnant and lactating women, and women with a history of or current Type I hypersensitivity.

Routine pharmacovigilance will be carried out for the important identified risks, ART-related effects, and important missing information.

Routine risk minimization activities include warnings and precautions or notification of undesirable effects in the EU Summary of Product Characteristics (EU SPC) for the important identified risks of hypersensitivity and injection site reactions, for all mentioned ART-related effects and for important missing information. No additional pharmacovigilance or risk minimization activities are planned.

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Table 1 List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ART	Assisted Reproductive Technology
ATC	Anatomical Therapeutic Chemical classification system
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CDC	Center for Disease Control
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COS	Controlled Ovarian Stimulation
CTD	Common Technical Document
EEA	European Economic Area
EMEA	European Medicines Agency
EU	European Union
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin Releasing Hormone
ICSI	Intracytoplasmic Sperm Injection
INN	International Nonproprietary Name
IVF	in vitro Fertilization
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
OHSS	Ovarian Hyperstimulation Syndrome
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
recFSH	Recombinant Follicle-Stimulating Hormone
RMP	Risk Management Plan
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SPC	Summary of Product Characteristics
USA	United States of America
WHO-ART	World Health Organization – Adverse Reactions Terminology

PRODUCT DETAILS

Table 2 provides the product details for ganirelix.

Table 2 Product Details

Invented name of the product (product short name):	Orgalutran
Active substance(s) (INN or common name):	ganirelix
Pharmacotherapeutic group (ATC Code):	H01CC01
Product Code (From EudraVigilance)	Anti-gonadotropin-releasing hormones (H01CC01)
Authorization procedure(s) (central, mutual recognition, decentralized, national)	Centralised Procedure
Name of Marketing Authorization Holder or Applicant:	N.V. Organon P.O. Box 20, Kloosterstraat 6, 5340 BH, Oss, The Netherlands
Date and country of first authorization worldwide	29 JUL 1999, USA
Date and country of first launch worldwide	MAY 2000, USA
Date and country of first authorization in the EEA	17 MAY 2000
Date and country of first launch in the EEA	01 JUL 2000, Germany
Total number of countries in which product is approved	86
Total number of countries in which product is launched	65

Abbreviations: ATC = Anatomical Therapeutic Chemical classification system, EEA = European Economic Area; INN = International Nonproprietary Name; USA = United States of America

Medical Dictionary for Regulatory Activities (MedDRA) versions: 11.1, 12.0, 14.1

Data lock point for this Risk Management Plan (RMP): 01 MAR 2012

Table 3 provides the product description for ganirelix.

Table 3 Product Description

Brief description of product (chemical class, mode of action etc)	Ganirelix is a synthetic decapeptide with a number of not naturally occurring amino acids to increase the half-life and has a high antagonistic activity to the GnRH receptor
Indication(s)	The prevention of premature luteinising hormone surges in women undergoing controlled ovarian hyperstimulation for assisted reproduction techniques.
Dosage	Subcutaneous, 0.25 mg once daily, starting on Day 5 or Day 6 of FSH administration up to (or up to and including) the day of triggering ovulation.
Pharmaceutical form(s) and strength(s)	Pre-filled syringe, containing 0.5 mL of solution for injection.

Abbreviations: FSH = follicle stimulating hormone; GnRH = gonadotropin releasing hormone

PART I

1.0 SAFETY SPECIFICATION

1.1 Nonclinical

1.1.1 Outline of Safety Concerns That Have Not Been Adequately Addressed by Clinical Data or Which are of Unknown Significance

Given the long-term product availability, very large patient exposure numbers, and accumulated safety data, any relationship to current human experience and safety is considered best exemplified by the current post-marketing exposure data and ongoing signaling measures.

Preclinical data reveal no special hazard for humans based on genotoxicity and acute, subchronic, and chronic toxicity studies.

Table 4 Safety Concerns From Nonclinical Studies

SAFETY CONCERN (from nonclinical studies)	RELEVANCE TO HUMAN USAGE
Reproduction studies carried out with ganirelix at doses of 0.1 to 10 ug/kg/day subcutaneously in the rat and 0.1 to 50 ug/kg/day subcutaneously in the rabbit showed increased litter resorption in the highest dose groups. No teratogenic effects were observed.	The relevance of these data for humans is unknown.
Toxicology studies carried out with ganirelix at doses of 0.1, 0.7 or 5.0 mg/kg/day subcutaneously in the cynomologus monkey and 0.1, 1.0 or 10 mg/kg/day in the rat showed signs of irritation at the injection site in a dose-dependent manner. In monkeys the signs consisted of swelling, discoloration and thickening; in rats the signs consisted of discoloration, encrustation and thickening. In monkeys, complete recovery occurred by 7-weeks post dosing.	Signs of irritation at the site of injection have been observed clinically.

1.1.2 Need for Additional Nonclinical Data for Use in Special Populations

Because there are no clinical safety issues and there has been no change in the patient population, no additional non-clinical studies are planned.

1.2 Clinical

1.2.1 Limitations of the Human Safety Database

Ganirelix in a dose of 0.25 mg has been marketed in the United States and the European Union (EU) since 2000 and is currently available in over 70 countries worldwide. The clinical development program of ganirelix (including local registration and postmarketing studies) encompassed 18 clinical trials. For this RMP, clinical (safety) data have been taken from the same trial set that has been used in 2005 to update Section 4.8 (Undesirable effects) of the ganirelix EU labeling (variation EMEA/H/C/000274/II/0011; Commission Decision October 25, 2005). The labeling was updated in order to reflect the requirement to code adverse events (AEs) with the MedDRA dictionary instead of World Health Organization – Adverse Reactions Terminology (WHO-ART), and was based on the safety data of the following six trials: 103001, 38602, 38607, 38608, 38616, and 38641. In addition, local tolerance was assessed in the following studies: controlled clinical studies (Studies 38607, 38616, and 103001) and uncontrolled clinical studies (Studies 38602, 38608 and 38649). Finally, data of follow-up Study 38644 have been incorporated to evaluate the risk of congenital anomalies in the offspring. These data are considered to adequately reflect the long established safety of ganirelix.

1.2.2 Exposure

1.2.2.1 Clinical Trial Exposure

Table 5 provides an overview of the trials included in the main, pooled safety evaluation with details per trial about the region, the year of trial start, and the number of subjects treated with ganirelix in these trials. The trial population consisted of females of infertile couples with an indication for Controlled Ovarian Stimulation (COS) prior to in vitro fertilization/ intracytoplasmic sperm injection (IVF/ICSI), at least ε18 years but δ39 years of age, with a body mass index between 18 and 29 kg/m^2, and with a normal menstrual cycle with a range of 24 to 35 days.

Table 5 Overview of Studies Applying RecFSH and Ganirelix (SCH 900761; Org 37462) Treatment for COS Prior to IVF or ICSI Included in This Summary Document

Study	Trial Description	Region	Start Date (year)	Number of Subjects
38602	A Phase 2, multi-center, double-blind, randomized, dose-finding study to assess the efficacy of the GnRH antagonist Org 37462 to prevent premature LH surges in women undergoing COH with recombinant FSH	Europe, Middle East	1996	332
38607	Phase 3, multi-center, open-label randomized study to assess the efficacy and safety of Org 37462 treatment in women undergoing COH, using a long protocol of buserelin as a reference treatment	Europe	1997	462
103001	Multi-center, open-label, randomized trial to assess the efficacy and safety using a long protocol of leuprolide acetate as a reference	North America	1997	197
38616	A Phase 3, multi-center, open-label, randomized study to assess the efficacy and safety of Org 37462 treatment in women undergoing COH, using a long protocol of triptorelin as a reference treatment	Europe, Middle East	1998	226
38608	A Phase 3, single-center, open-label study to assess safety of Org 37462 in women undergoing multiple treatment cycles for COH	Middle East (Israel)	1998	167
38641	Open-label, multi-center, randomized trial in women undergoing COH for IVF or ICSI to evaluate the pharmacokinetic and pharmacodynamic pattern of Org 37462 (ganirelix) treatment after weight adjusted dosing, using a fixed-dose Org 37462 regimen as a reference treatment	Europe, Middle East	2000	205

Abbreviations: COS (COH) = controlled ovarian stimulation; FSH = follicle stimulating hormone; GnRH = gonadotropin releasing hormone; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; LH = luteinising hormone' recFSH = recombinant follicular-stimulating hormone

Note that Studies 38602 and 38641 included various ganirelix doses.

The demographic characteristics of the subjects are presented in **Table 6**.

Table 6 Demographic Characteristics of Subjects

Characteristic	Statistic	All Subjects[a] (N=1589)
Age (years)	n Mean (SD) Median (Min - Max)	1589 31.4 (4.1) 32.0 (18, 42)
Body height (cm)	n Mean (SD) Median (Min - Max)	1587 164.8 (7.1) 165.0 (142, 190)
Body weight (kg)	n Mean (SD) Median (Min - Max)	1585 63.6 (10.3) 62.0 (42, 143)
Body mass index (kg/m²)	n Mean (SD) Median (Min - Max)	1584 23.4 (3.5) 22.9 (16, 46)
Region, n (%)	Europe Middle East North America	1007 (63.4) 385 (24.2) 197 (12.4)
Race, n (%)	Asian Black Caucasian Other	21 (1.3) 21 (1.3) 1533 (96.5) 14 (0.9)

Abbreviations: max = maximum; min = minimum; SD = standard deviation
[a] Includes studies 38602, 38607, 103001, 38616, 38608, and 38641

The applied exclusion criteria listed below were used across all studies:

1. History of/or any current (treated) endocrine abnormality;
2. History of/or current polycystic ovary syndrome (not applied for Protocol 38608);
3. History of non- or low ovarian response to FSH/human menopausal gonadotropin treatment;
4. Any clinically relevant abnormal laboratory value based on a sample taken during the screening phase (including Papanicolaou smear);
5. Contraindications for the use of gonadotropins (eg, tumors, pregnancy/lactation, undiagnosed vaginal bleeding, hypersensitivity, ovarian cysts);
6. Recent history of/or current epilepsy, human immunodeficiency virus infection, diabetes, cardiovascular, gastro-intestinal, hepatic, renal or pulmonary disease;
7. History of/or current Type I hypersensitivity (urticaria, eczema, hay fever, asthma);
8. Hypertension or currently treated hypertension;
9. Administration of investigational drugs within 3 months prior to signing informed consent.

1.2.2.2 Epidemiological Study Exposure

No epidemiological studies have been performed or are currently ongoing.

1.2.2.3 Post Marketing (Nonstudy) Exposure

Worldwide patient exposure for ganirelix for the reporting period 01 JAN 2000 through 31 DEC 2011 was estimated from unit sales data provided by IMS Health MIDAS market research database. Ganirelix is available in syringes of 0.25 mg/0.5 mL solution for injection.

From 01 JAN 2000 until 31 DEC 2011, 5,860,796 syringes of ganirelix were distributed worldwide. Based on the IMS Health sales data and the assumption that five syringes are needed for one treatment cycle, ganirelix has been used in approximately 1,172,159 cycles during the reporting period.

1.3 Populations Not Studied in the Preauthorization Phase

The exclusion criteria as defined in **Section 1.2** have led to the following EU SPC restrictions:

- The safety and efficacy of ganirelix have not been established in women weighing less than 50 kg or more than 90 kg.
- The use of ganirelix is contraindicated during pregnancy and lactation.
- The use of ganirelix is contraindicated in women with moderate or severe impairment of renal or hepatic function.
- Special care should be taken in women with signs and symptoms of active allergic conditions. In the absence of clinical experience, ganirelix treatment is not advised in women with severe allergic conditions.

1.4 Postauthorization Experience

1.4.1 Projected Postauthorization Usage Data

Not applicable.

1.4.2 Actual Postauthorization Usage Data

Refer to **Section 1.2.2.3** Postmarketing (Nonstudy) Exposure.

1.4.3 Regulatory Action Taken

There have been no regulatory actions related to Ganirelix that resulted in marketing authorization withdrawal or suspension, failure to obtain marketing authorization renewal, restriction on distribution, clinical trial suspension, dosage modification, change in target population or pharmaceutical changes for safety reasons.

1.5 Adverse Events/Adverse Reactions

1.5.1 Newly Identified Safety Concerns

No new safety concerns have been identified.

1.5.2 Details of Important Identified and Potential Risks

1.5.2.1 Details of Important Identified Risks

Table 7	**Details of Important Identified Risks**
Identified Risk Hypersensitivity reactions	MedDRA SMQ: Anaphylactic reaction (narrow)
Frequency/ Seriousness/ outcomes	Review of data from the clinical program of ganirelix (adverse events within the SMQ anaphylactic reaction, immunogenicity results, and local tolerance scores after ganirelix injection) as well as postmarketing data (adverse events within the SMQ anaphylactic reaction) does not suggest a specific safety concern in terms of a hypersensitivity reactions or anti-ganirelix antibody formation after ganirelix administration.
	Clinical data: *Adverse Events within the SMQ Anaphylactic Reaction* There were no cases identified in the clinical program, that fall under the SMQ anaphylactic reaction.
	Immunogenicity One Phase 3 trial was performed in which the safety of repeated ganirelix treatment in women undergoing COS was assessed (Study 38608). A total of 171 subjects were randomized, 167 subjects had received at least one dose of ganirelix, of whom 79 subjects had entered a second treatment cycle and 30 subjects a third treatment cycle with ganirelix. At least one posttreatment sample was assessed for 163 first-treatment cycles, 77 second-treatment cycles, and 30 third-treatment cycles (for some subjects, not all samples were available). All samples were negative both for total immunoglobulin G and for immunoglobulin E anti-ganirelix antibodies.

<table>
<tr><td>Table 7</td><td colspan="2">Details of Important Identified Risks</td></tr>
<tr><td></td><td colspan="2">Post-marketing data:

The safety database was searched for spontaneous events from the search criteria listed above received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012.

<table><tr><th>PT</th><th>Number of Events</th></tr><tr><td>Anaphylactoid reaction</td><td>2</td></tr><tr><td>Anaphylactic reaction</td><td>1</td></tr><tr><td>Anaphylactic shock</td><td>1</td></tr></table></td></tr>
<tr><td>Severity and nature of risk</td><td colspan="2">Unknown</td></tr>
<tr><td>Background incidence/prevalence</td><td colspan="2">A drug-related hypersensitivity reaction can only occur after administration of the drug.</td></tr>
<tr><td>Risk groups or risk factors</td><td colspan="2">Special care should be taken in women with signs and symptoms of active allergic conditions. In the absence of clinical experience, ganirelix treatment is not advised in women with severe allergic conditions.</td></tr>
<tr><td>Potential mechanisms</td><td colspan="2">Based on the fact that GnRH antagonists are known to cause mast cell degranulation, they may cause hypersensitivity responses at the site of injection.</td></tr>
<tr><td>Preventability</td><td colspan="2">Partially by avoidance of treatment in patients with known hypersensitivity.</td></tr>
<tr><td>Potential public health impact of safety concern</td><td colspan="2">None</td></tr>
<tr><td>Evidence source</td><td colspan="2">PSUR</td></tr>
<tr><td>Regulatory action taken</td><td colspan="2">Ganirelix is always used together with other drugs (gonadotropins) as part of an ovarian stimulation procedure to grow and collect mature oocytes for subsequent in vitro fertilization. As a consequence one should be very careful to attribute AEs, including SAEs, either to ganirelix and/or these preparations of gonadotropins. Nevertheless, since ganirelix' International Birth Date (July 1999, approved in the USA) a few reports were received at the Global Pharmacovigilance department suggesting that possibly allergic reactions in patients administered ganirelix together with an FSH preparation were caused by the use of ganirelix. Based on these reports the CHMP made their request to add a sentence on allergic reactions to the EU SPC:

"Very rarely cases of hypersensitivity reactions including various symptoms such as rash, facial swelling and dyspnea have been reported among patients administered Orgalutran with FSH".</td></tr>
</table>

Abbreviations: AE = adverse event; CHMP = Committee for Medicinal Products for Human Use; COS = Controlled Ovarian Stimulation; CTD = Common Technical Document; EU = European Union; FSH = follicle stimulating hormone; MedDRA = Medical Dictionary for Regulatory Activities; PSUR = Periodic Safety Update Report; SAE = serious adverse event; SC = subcutaneous; SMQ = Standardized MedDRA Query; SPC = Summary of Product Characteristics; USA = United State of America

Table 8 Details of Important Identified Risks

Identified Risk Injection site reaction	MedDRA PTs for injection site reaction footnoted below[1]
Frequency/ Seriousness/ outcomes	Review of data from the clinical program of ganirelix (local tolerance scores after ganirelix injection) as well as postmarketing does not suggest a specific safety concern after ganirelix administration.
	Clinical data: Local tolerance (subcutaneous injection site reactions) was assessed in the following studies: controlled clinical studies (Studies 38607, 38616, and 103001) and uncontrolled clinical studies (Studies 38602, 38608, and 38649). The presence and maximum intensity (none, mild, moderate, or severe) of five injection site reactions (itching, pain, bruising, swelling, and redness) at 1, 4, and 24 hours after daily injection were assessed. None of the injection site reactions was reported as a serious adverse event. All subjects recovered from the injection site reactions. In the following table, the number (percentage) of subjects with at least a moderate and a severe reaction is tabulated by time point, and compared with GnRH agonists (leuprolide and triptorelin). At 1 hour after injection, 14.1% of subjects treated with ganirelix showed a moderate reaction on any of the local tolerance parameters, and 0.9% showed a severe reaction. Both in the leuprolide group (24.4% and 1.1%, respectively) and in the triptorelin group (20.4% and 3.7%, respectively), these percentages were noticeably higher. In the ganirelix group, the percentage of subjects with a moderate or severe reaction 4 or 24 hours after injection dropped below 5%, whereas in the GnRH agonist groups, the percentages remained above 5% or even 10% at these time points.
	Incidences of Local Tolerance by Time After Injection (Studies 38607, 38616, 103001, 38602, 38608, and 38649) Restricted to the Subjects Treated With Ganirelix

[1] Administration site pain, Induration, Local swelling, Localised oedema, Skin induration, Subcutaneous nodule Application site abscess, Application site alopecia, Application site anaesthesia, Application site atrophy, Application site bleeding, Application site burn, Application site cellulitis, Application site cold feeling, Application site dermatitis, Application site discharge, Application site discolouration, Application site discomfort, Application site dryness, Application site eczema, Application site erosion, Application site erythema, Application site exfoliation, Application site fissure, Application site folliculitis, Application site haematoma, Application site hyperaesthesia, Application site hypersensitivity, Application site induration, Application site infection, Application site inflammation, Application site irritation, Application site mass, Application site necrosis, Application site nodule, Application site odour, Application site oedema, Application site pain, Application site pallor, Application site papules, Application site paraesthesia, Application site perspiration, Application site photosensitivity reaction, Application site pruritus, Application site pustules, Application site rash, Application site reaction, Application site scab, Application site scar, Application site swelling, Application site ulcer, Application site urticaria, Application site vesicles, Application site warmth, Injection site abscess, Injection site abscess sterile, Injection site anaesthesia, Injection site atrophy, Injection site calcification, Injection site cellulitis, Injection site coldness, Injection site cyst, Injection site dermatitis, Injection site discharge, Injection site discolouration, Injection site discomfort, Injection site dryness, Injection site dysaesthesia, Injection site eczema, Injection site erosion, Injection site erythema, Injection site exfoliation, Injection site extravasation, Injection site fibrosis, Injection site haematoma, Injection site haemorrhage, Injection site hypersensitivity, Injection site hypertrophy, Injection site induration, Injection site infection, Injection site inflammation, Injection site injury, Injection site irritation, Injection site ischaemia, Injection site joint effusion, Injection site joint inflammation, Injection site joint movement impairment, Injection site joint pain, Injection site joint redness, Injection site joint swelling, Injection site joint warmth, Injection site laceration, Injection site lymphadenopathy, Injection site macule, Injection site mass, Injection site movement impairment, Injection site necrosis, Injection site nerve damage, Injection site nodule, Injection site oedema, Injection site pain, Injection site pallor, Injection site papule, Injection site paraesthesia, Injection site phlebitis, Injection site photosensitivity reaction, Injection site pruritus, Injection site pustule, Injection site rash, Injection site reaction, Injection site recall reaction, Injection site scab, Injection site scar, Injection site streaking, Injection site swelling, Injection site thrombosis, Injection site ulcer, Injection site urticaria, Injection site vasculitis, Injection site vesicles, Injection site warmth

Table 8 Details of Important Identified Risks

Parameters		Ganirelix		Leuprolide		Triptorelin	
		Moderate	Severe	Moderate	Severe	Moderate	Severe
Time after Injection		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Itching	1 hr 4 hrs 24 hrs	22 (1.4) 2 (0.2) 2 (0.1)	4 (0.2) 0 0	5 (5.6) 0 0	1 (1.1) 0 0	6 (5.6) 1 (1.0) 1 (1.0)	0 0 0
Pain	1 hr 4 hrs 24 hrs	45 (2.8) 6 (0.7) 7 (0.4)	1 (0.1) 0 1 (0.1)	4 (4.4) 0 0	1 (1.1) 0 0	10 (9.3) 4 (3.8) 2 (1.9)	1 (0.9) 0 1 (1.0)
Bruising	1 hr 4 hrs 24 hrs	20 (1.2) 13 (1.5) 43 (2.7)	1 (0.1) 2 (0.2) 5 (0.3)	4 (4.4) 4 (4.4) 10 (11.1)	1 (1.1) 0 0	9 (8.3) 10 (9.5) 11 (10.5)	1 (0.9) 1 (1.0) 2 (1.9)
Swelling	1 hr 4 hrs 24 hrs	91 (5.7) 12 (1.4) 6 (0.4)	5 (0.3) 2 (0.2) 0	14 (15.6) 1 (1.1) 1 (1.1)	1 (1.1) 0 0	6 (5.6) 3 (2.9) 0	3 (2.8) 1 (1.0) 1 (1.0)
Redness	1 hr 4 hrs 24 hrs	146 (9.1) 2 (0.2) 9 (0.6)	8 (0.5) 1 (0.1) 0	6 (6.7) 0 0	1 (1.1) 0 0	9 (8.3) 3 (2.9) 2 (1.9)	2 (1.9) 1 (1.0) 1 (1.0)
Any Reaction	1 hr 4 hrs 24 hrs	226 (14.1) 29 (3.5) 55 (3.4)	14 (0.9) 3 (0.4) 6 (0.4)	22 (24.4) 5 (5.6) 11 (12.2)	1 (1.1) 0 0	22 (20.4) 16 (15.2) 12 (11.4)	4 (3.7) 1 (1.0) 3 (2.9)
n: number of subjects with local tolerance reactions at the specified time and severity.							

Table 8 Details of Important Identified Risks

	Post-marketing data: The safety database was searched for spontaneous events of injection site reactions[2] from the search criteria listed above received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012.

PT	Number of Events
Application site erythema	1
Application site warmth	1
Injection site cellulitis	2
Injection site eczema	1
Injection site erythema	25
Injection haematoma	3
Injection site haemorrhage	2
Injection site hypersensitivity	2
Injection site inflammation	2
Injection site irritation	1
Injection site oedema	1
Injection site pain	17
Injection site pruritis	7
Injection site rash	5
Injection site reaction	13
Injection site swelling	8
Injection site urticaria	3
Injection site warmth	3
Total Events	97
Total ICSRs	71

[2] Administration site pain, Induration, Local swelling, Localised oedema, Skin induration, Subcutaneous nodule Application site abscess, Application site alopecia, Application site anaesthesia, Application site atrophy, Application site bleeding, Application site burn, Application site cellulitis, Application site cold feeling, Application site dermatitis, Application site discharge, Application site discolouration, Application site discomfort, Application site dryness, Application site eczema, Application site erosion, Application site erythema, Application site exfoliation, Application site fissure, Application site folliculitis, Application site haematoma, Application site hyperaesthesia, Application site hypersensitivity, Application site induration, Application site infection, Application site inflammation, Application site irritation, Application site mass, Application site necrosis, Application site nodule, Application site odour, Application site oedema, Application site pain, Application site pallor, Application site papules, Application site paraesthesia, Application site perspiration, Application site photosensitivity reaction, Application site pruritus, Application site pustules, Application site rash, Application site reaction, Application site scab, Application site scar, Application site swelling, Application site ulcer, Application site urticaria, Application site vesicles, Application site warmth, Injection site abscess, Injection site abscess sterile, Injection site anaesthesia, Injection site atrophy, Injection site calcification, Injection site cellulitis, Injection site coldness, Injection site cyst, Injection site dermatitis, Injection site discharge, Injection site discolouration, Injection site discomfort, Injection site dryness, Injection site dysaesthesia, Injection site eczema, Injection site erosion, Injection site erythema, Injection site exfoliation, Injection site extravasation, Injection site fibrosis, Injection site haematoma, Injection site haemorrhage, Injection site hypersensitivity, Injection site hypertrophy, Injection site induration, Injection site infection, Injection site inflammation, Injection site injury, Injection site irritation, Injection site ischaemia, Injection site joint effusion, Injection site joint inflammation, Injection site joint movement impairment, Injection site joint pain, Injection site joint redness, Injection site joint swelling, Injection site joint warmth, Injection site laceration, Injection site lymphadenopathy, Injection site macule, Injection site mass, Injection site movement impairment, Injection site necrosis, Injection site nerve damage, Injection site nodule, Injection site oedema, Injection site pain, Injection site pallor, Injection site papule, Injection site paraesthesia, Injection site phlebitis, Injection site photosensitivity reaction, Injection site pruritus, Injection site pustule, Injection site rash, Injection site reaction, Injection site recall reaction, Injection site scab, Injection site scar, Injection site streaking, Injection site swelling, Injection site thrombosis, Injection site ulcer, Injection site urticaria, Injection site vasculitis, Injection site vesicles, Injection site warmth

Table 8 Details of Important Identified Risks

Severity and nature of risk	Unknown
Background incidence/prevalence	A drug-related injection site reaction can only occur after administration of the drug.
Risk groups or risk factors	Special care should be taken in women with signs and symptoms of active allergic conditions. In the absence of clinical experience, ganirelix treatment is not advised in women with severe allergic conditions.
Potential mechanisms	Based on the fact that GnRH antagonists are known to cause mast cell degranulation, they may cause hypersensitivity responses at the site of injection.
Preventability	Partially by avoidance of treatment in patients with known hypersensitivity.
Potential public health impact of safety concern	None
Evidence source	PSUR
Regulatory action taken	None

Abbreviations: AE = adverse event; CHMP = Committee for Medicinal Products for Human Use; COS = Controlled Ovarian Stimulation; CTD = Common Technical Document; EU = European Union; FSH = follicle stimulating hormone; MedDRA = Medical Dictionary for Regulatory Activities; PSUR = Periodic Safety Update Report; SAE = serious adverse event; SC = subcutaneous; SMQ = Standardized MedDRA Query; SPC = Summary of Product Characteristics; USA = United State of America

1.5.2.2 Details of Important Potential Risks

Not applicable.

1.6 Identified and Potential Interactions With Other Medicinal Products, Food and Other Substances

Interactions of ganirelix with other medicines have not been investigated; interactions with commonly used medicinal products can therefore not be excluded.

1.7 Epidemiology of the Indication(s) and Important Adverse Events

1.7.1 Incidence, Prevalence, Mortality, and Demographic Profile of the Target Population

The incidence, prevalence, mortality and demographic profile of the target population is provided in **Table 9**.

Table 9 Incidence, Prevalence, Mortality and Demographic Profile of the Target Population

Indication/target population	Controlled ovarian stimulation prior to IVF or ICSI
Incidence of target indication	Not available since the population at risk is not known. Prevalence data are the measure of disease frequency for infertility.
Prevalence of target indication	International estimates of infertility prevalence and treatment-seeking were recently presented.[Ref. 5.4: 5] These estimates were based on 25 population surveys on the prevalence of infertility, published since 1990, sampling 172,413 women. The 12-month prevalence ranged from 3.5%-16.7% in more developed countries and from 6.9%-9.3% in less developed countries. In 17 studies sampling 6,410 women, the proportion of couples seeking medical care was 56.1% (range 42%-76.3%) in more developed countries and 51.2% (range 27%-74.1%) in less developed countries. In more developed countries, the proportion of people actually receiving care was 22.4% (four studies). In Europe, in 2005, a mean number of four treatment cycles were done per 1,000 women of reproductive age per year. Overall, in those countries were all clinics reported to the national register in 2005, 258,516 cycles were undertaken in a population of 274.2 million, giving a mean of 1,115 cycles per million.[Ref. 5.4: 3] The number of ART cycles reported in the USA in 2006 was 138,198.[Ref. 5.4: 7]
Mortality in target indication	The target population consists of patients with an indication for controlled ovarian stimulation prior to IVF or ICSI but otherwise healthy. It is not expected that mortality rates are higher in the infertile population compared to the total female population of fertile age. A study in a cohort of 29,700 Australian IVF patients comparing the mortality rates of women who received IVF treatment (n=21,086) as well as women who were referred but not treated (n=8,614) with the mortality rate in the general female population found that allcause mortality rates in IVF patients (treated and untreated) were significantly lower than in the general female population of the same age.[Ref. 5.4: 12] The standardized mortality ratio was 0.58 (95% CI 0.48-0.69) in IVF treated women and 0.62 (95% CI 0.50-0.77) in untreated women. Although these results are reassuring with regard to the safety of IVF treatment, these findings may indicate that selection processes are occurring where the unhealthiest women in the population are deterred from pregnancy and infertility treatment (healthy patient effect).
Potential health risk	Not applicable since the target population consists of patients with an indication for COS prior to IVF or ICSI but are otherwise healthy.

Table 9 Incidence, Prevalence, Mortality and Demographic Profile of the Target Population

Demographic profile of target population	The age distribution of women receiving IVF in Europe in 2005 was δ29 years 15.7%, 30-34 years 33.2%, 35-39 years 35.1%, 40-44 years 14.6%, ε45 years 0.8% and of women receiving ICSI was δ29 years 18.8%, 30-34 years 35.4%, 35-39 years 32.3%, 40-44 years 11.8%, and ε45 years 1.2%.[Ref. 5.4: 3] In the USA, the age distribution of women using ART in 2006 was <35 years 39.4%, 35-37 years 22.5%, 38-40 years 18.8%, 41-42 years 9.6% and >42 years 9.8%.[Ref. 5.4: 7]

Abbreviations: ART = assisted reproductive technology; CI = confidence interval; COS = controlled ovarian stimulation; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; USA = United States of America

1.7.2 Important Comorbidity in the Target Population

Important comorbidity in the target population is provided in **Table 10**.

Table 10 Important Comorbidity in the Target Population

Patients with an indication for controlled ovarian stimulation prior to IVF or ICSI	The majority of the target population consists of patients with an indication for COS prior to IVF or ICSI and otherwise healthy. Certain risk factors attributing to the subfertility also have an impact on the health of the patient in general (eg, obesity, smoking, body weight, age, socio-economical class, education, diabetes, thyroid dysfunction, asthma, autoimmune diseases etc.). The inability to conceive children is associated with significant psychosocial consequences for many women and their partners.[Ref. 5.4: 11, 13] Infertility patients experience high levels of distress and their level of anxiety and depression is equivalent to that experienced by women with cancer or heart disease.[Ref. 5.4: 18] The IVF treatment process itself is increasingly recognized as contributing to the physical, psychologic, and emotional burden on infertility patients.[Ref. 5.4: 4, 24]
Abbreviations: COS = controlled ovarian stimulation; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization	

1.7.3 Epidemiology of the Risk in the Target Population When Unexposed to the Product

Epidemiology of the risks in the target population when unexposed to the ganirelix are provided in **Table 11** and **12**

Table 11 Epidemiology of the Risk in the Target Population When Unexposed to the Product

Identified risk	Hypersensitivity reactions
Incidence of condition	A drug-related hypersensitivity reaction can only occur after administration of the drug.
Prevalence of condition	A drug-related hypersensitivity reaction can only occur after administration of the drug.
Mortality of condition	Fatal drug-related hypersensitivity reactions can only occur after administration of the drug.

Table 12 Epidemiology of the Risk in the Target Population When Unexposed to the Product

Identified risks	Injection site reactions
Incidence of condition	A drug-related injection site reaction can only occur after administration of the drug.
Prevalence of condition	A drug-related injection site reaction can only occur after administration of the drug.
Mortality of condition	A drug-related injection site reaction can only occur after administration of the drug.

1.8 ART-Related Events

In **Table 13**, the safety concerns are discussed that are related to the target population undergoing ART treatment and/or to the ART treatment and the resulting pregnancy and/or the pharmacological class. The major risk associated with proper use of GnRH antagonists is hypersensitivity. This has already been discussed in **Section 1.5.2.1** and will not be further discussed here.

Table 13 Pharmacological Class Effects

<table>
<tr><th>Risk</th><th>Frequency in Clinical Trials of Product</th><th>Frequency Seen With Other Products in Same Pharmacological Class (Source of Data/Journal Reference)</th><th>Comment</th></tr>
<tr><td>Ovarian hyperstimulation syndrome</td><td>An incidence of 3.5% is reported in the pooled clinical ganirelix trials</td><td>The variety of grading systems for OHSS severity, as well as inclusion of different patient populations and treatment regimens has made it difficult to compare incidences of OHSS reported in literature. Therefore, the incidence of mild OHSS ranged from 8% to 33% of stimulated cycles, the incidence of moderate OHSS varied from 3% to 6% and of severe OHSS from 0.1% to 2%.[Ref. 5.4: 8] It has been described in the literature that patients treated with a long GnRH agonist protocol have a higher risk of developing OHSS than patients treated with a GnRH antagonist protocol.[Ref. 5.4: 16]</td><td>OHSS is related to treatment with gonadotropins. GnRH agonists or antagonists can not cause OHSS.</td></tr>
<tr><td></td><td colspan="3">Post-marketing Data
The safety database was searched for spontaneous events with a MedDRA PT of ovarian hyperstimulation syndrome received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012.
<table><tr><th>PT</th><th>Number of Events</th></tr><tr><td>Ovarian hyperstimulation syndrome</td><td>19</td></tr></table></td></tr>
<tr><td>Congenital malformations</td><td>Information on congenital malformations was reported in follow-up Studies 38603, 103-002, 38614, 38615, and 38625 (Phase 2-3 development program) and Study 38644 (Phase 4 follow-up)
Using the broad definition for classification of major malformations in infants ≥26 weeks gestational age (a condition that causes functional impairment or requires surgical correction), the overall incidence of major malformations was 4.6% in the ganirelix group. The total incidence rate of infants with at least one minor congenital</td><td>In the follow-up studies from the clinical trial program, the overall incidence of major malformations in infants ε26 weeks of gestational age was 5.1% in the GnRH agonist treatment group when the broad definition was applied. The total incidence rate of infants with at least one minor congenital malformation was 2.2% and 27.3% in the GnRh agonist group for the Phase 2-3 and Phase 4 follow-up cohorts, respectively, resulting in an overall minor malformation rate of 23.4%. The total malformation rate taking into account major malformations in stillborns, in terminations and in liveborns is approximately 4.5%. Restricted to the liveborns after IVF or ICSI procedures, major congenital malformations are reported for 3%-4%. In addition, 5%-10% of the children born after IVF or ICSI were</td><td>Note that in the Clinical Study Phase 4 follow-up data set all birth defects identified, regardless of clinical relevance, are presented and used for the calculation of incidences and malformation rates.</td></tr>
</table>

Table 13 Pharmacological Class Effects

	malformation was 3.8% and 37.9% in the ganirelix group for the Phase 2-3 and Phase 4 follow-up cohorts, respectively, resulting in an overall minor malformation rate of 27.6%.	reported to have minor malformations at birth, which increased to 14%-17% when examined again 2 months after. [Ref. 5.4: 6]	
	Post-marketing Data The safety database was searched for spontaneous events from the MedDRA SMQ Congenital, familial, and genetic disorders received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012. There were no spontaneous events[3] from the above mentioned SMQ.		
Multiple pregnancy	In the clinical trial program, multiple pregnancy rates after ganirelix treatment ranged between 17.2% and 38.9%.	In the clinical trial program, multiple pregnancy rates after GnRH agonist treatment ranged between 28.2% and 44.4%.	Note that the multiple pregnancy rate is primarily dependent on the number of embryos transferred. Over the years, clinical practice is changing in that single embryo transfer is becoming more accepted.
	Post-marketing Data The safety database was searched for spontaneous events with a MedDRA PT of multiple pregnancy or twin pregnancy and for the following words in a narrative search "twin", "triplet", "quadruplet", "multiple pregnancy", "multiple birth" and "multiple gestation" received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012. There were 4 reports of multiple pregnancy from the above mentioned criteria.		
Spontaneous abortion	An incidence of 4.0% is found in the pooled clinical ganirelix trials.	Spontaneous abortion is one of the most frequent complications during pregnancy. Results from ART registries report that a spontaneous abortion occurs in around 15% of pregnancies after ART cycles. [Ref. 5.4: 15]	Note that comparison to literature data is hampered by the fact that definitions of spontaneous abortion vary between clinics and countries and are dependent on timing and accurateness of the biochemical pregnancy test or other diagnostic evaluation applied.

[3] One ICSR [redacted] was identified in which a report of intra-uterine death was reported with "birth defects"; however, no congenital anomalies were specified and no additional information was provided.

Table 13 Pharmacological Class Effects

<table>
<tr><td></td><td colspan="3">Post-marketing Data
The safety database was searched for spontaneous events from the MedDRA SMQ Termination of pregnancy and risk of abortion received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012.

<table><tr><th>PT</th><th>Number of Events</th></tr><tr><td>Abortion spontaneous</td><td>2</td></tr><tr><td>Intra-uterine death</td><td>1</td></tr></table></td></tr>
<tr><td>Ectopic pregnancy</td><td>The incidence in the pooled clinical ganirelix trials is 0.9%.</td><td>The reported incidence of ectopic pregnancies in women undergoing fertility treatment was 2.2% to 3.4% of the clinical pregnancies.[Ref. 5.4: 9]</td><td></td></tr>
<tr><td></td><td colspan="3">Post-marketing Data
The safety database was searched for spontaneous events with a MedDRA PT of ectopic pregnancy, abortion of ectopic pregnancy, ectopic pregnancy termination, ectopic pregnancy with intrauterine device, or Ruptured ectopic pregnancy received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012.

<table><tr><th>PT</th><th>Number of Events</th></tr><tr><td>Ruptured ectopic pregnancy</td><td>1</td></tr></table>This one report of ruptured ectopic pregnancy concerned the rupture of one embryo of a triplet pregnancy.</td></tr>
<tr><td>Ovarian torsion</td><td>The incidence in the pooled clinical ganirelix trials is 0.1%.</td><td>Reported incidences of ovarian torsions during IVF vary between 0.1% and 0.2%,[Ref. 5.4: 10, 14, 26]</td><td></td></tr>
<tr><td></td><td colspan="3">Post-marketing Data
The safety database was searched for spontaneous events with a MedDRA PT of ovarian torsion received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012. There were no spontaneous events of ovarian torsion.</td></tr>
<tr><td>Venous thromboembolism</td><td>Venous thromboembolism is not reported during the in treatment period in the pooled clinical ganirelix trials.</td><td>The incidence of venous thromboembolic events alone, in women undergoing IVF, has been estimated to be 0.08% to 0.11% of treatment cycles from at least two fertility centers.[Ref. 5.4: 23, 30]</td><td>The association between venous thromboembolic events and ART arises primarily within the context of OHSS. Often also other predisposing factors are found, like inherited thrombophilia and (multiple) pregnancy.</td></tr>
</table>

Table 13 Pharmacological Class Effects

<table>
<tr><td></td><td colspan="3">Post-marketing Data
The safety database was searched for spontaneous events from the MedDRA SMQ Embolic and thrombotic events, venous or Broad SMQ thrombophlebitis received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012.
<table><tr><th>PT</th><th>Number of Events</th></tr><tr><td>Deep vein thrombosis</td><td>1</td></tr><tr><td>Thrombosis</td><td>1</td></tr></table></td></tr>
<tr><td>Malignant neoplasm</td><td>Malignant neoplasm is not reported during the in treatment period in the pooled clinical ganirelix trials.</td><td>Based on the data currently available, [Ref. 5.4: 21, 22, 27, 28] there is no epidemiological evidence for an increased risk of gynecological cancers due to the ART procedure or the specific drugs used in ART despite the theoretical concerns about the elevated levels of ovarian hormones in these women.</td><td>Although the concern exists that exogenous hormones might play a role in the development of ovarian and other reproductive neoplasms in infertile women, the data currently available do not demonstrate an increased risk.</td></tr>
<tr><td></td><td colspan="3">Post-marketing Data
The safety database was searched for spontaneous events from the MedDRA SMQ Ovarian, neoplasms, malignant and unspecified OR Uterine and fallopian tube neoplasms, malignant and unspecified received by the MAH from HCPs from market introduction of ganirelix to 01-Mar-2012. There were no spontaneous events of malignant neoplasms from the above mentioned SMQs.</td></tr>
</table>

Abbreviations: ART = assisted reproductive technology; CDC = Center for Disease Control; GnRH = gonadotropin releasing hormone; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OHSS = ovarian hyperstimulation syndrome; recFSH = recombinant follicle-stimulation hormone; US = United States of America

1.9 Additional Requirements

1.9.1 Potential for Overdose

Overdosage in humans may result in a prolonged duration of action. In case of overdose, ganirelix treatment should be (temporarily) discontinued. No data on acute toxicity of ganirelix in humans are available but it is unlikely that toxic effects will occur. Clinical studies with subcutaneous administration of ganirelix at single doses up to 12 mg did not show systemic undesirable effects. In acute toxicity studies in rats and monkeys non-specific toxic symptoms were only observed after intravenous administration of ganirelix over 1 and 3 mg/kg, respectively.

1.9.2 Potential for Transmission of Infectious Agents

The potential of ganirelix for transmission of infectious agents is very low because of the following reasons:

- The active substance ganirelix is a synthetic decapeptide.
- All excipients of ganirelix are from chemical origin and are therefore not susceptible for transmitting infectious agents.

1.9.3 Potential for Misuse for Illegal Purposes

In view of the specific mechanism of action of ganirelix, no potential for misuse for illegal purposes exists.

1.9.4 Potential for Off-Label Use

Use of Ganirelix in Patients With Allergic Conditions.

Ganirelix has not been studied in women with signs and symptoms of active allergic conditions. These patients may be especially prone for the aggravation of hypersensitivity reactions.

The following warnings and precautions are included in the EU SPC Section 4.4 (Special warnings and precautions for use):

- Special care should be taken in women with signs and symptoms of active allergic conditions. In the absence of clinical experience, ganirelix treatment is not advised in women with severe allergic conditions.

In addition, the following contraindications are included in the EU SPC Section 4.3 (Contraindications):

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to gonadotropin-releasing hormone (GnRH) or any other GnRH analogue.

Use of Ganirelix in Patients With Moderate or Severe Impairment of Renal or Hepatic Function.

Ganirelix has not been studied in women with moderate or severe impairment of renal or hepatic function. The majority of the target population consists of patients with an indication for controlled ovarian stimulation prior to IVF or ICSI but otherwise healthy. Although it is very unlikely that a patient with moderate or severe renal or hepatic impairment would undergo ART treatment, the following contraindications are included in the EU SPC Section 4.3 (Contraindications):

- Moderate or severe impairment of renal or hepatic function.

Use in Male Patients.

Ganirelix is not indicated for use in male patients.

Use of Ganirelix During Pregnancy or Lactation

No clinical data on ganirelix exposure during pregnancy or lactation are available. Although it is very unlikely that a pregnant or lactating patient might start ART, the following contraindications are included in the EU SPC Section 4.3 (Contraindications):

- Pregnancy or lactation.

The following text is included in the EU SPC Section 4.6 (Pregnancy and lactation):

- No clinical data on exposed pregnancies are available.
- In animals, exposure to ganirelix at the time of implantation resulted in litter resorption (see 5.3 Preclinical safety data). The relevance of these data for humans is unknown.
- 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 Contraindications).

In the EU SPC Section 5.3 (Preclinical safety data) the following information is included:

- 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.

Post-marketing data

From market introduction to 01-Mar-2012, 2 ICSRs of exposure during pregnancy (1 Health Care Provider and 1 consumer report) and 1 ICSR of drug exposure via breast milk were identified (Health Care Provider).

In 1 ICSR of drug exposure during pregnancy[4], the patient inadvertently received an injection of orgalutran instead of enoxaparin at approximately 3-months gestation. The patient carried her pregnancy to full term and had a normal healthy newborn. In the 1 remaining ICSR[5] of exposure during pregnancy, the patient was exposed at 4 weeks gestation; however, outcome of the pregnancy was not provided.

The 1 ICSR[6] concerning drug exposure via breast milk described a patient that was breastfeeding who initiated therapy with orgalutran. No ADRs were reported for the infant as a result of the exposure during lactation.

Use of Ganirelix in the Treatment of Hot Flashes

Ganirelix is not indicated in women for the treatment of hot flashes. [Ref. 5.4: 25]

4 [redacted]
5
6

1.9.5 Potential for Off-Label Pediatric Use

It is generally acknowledged that the therapeutic indication for ganirelix is not applicable for girls below the age of 18 years.

1.10 Summary - Ongoing Safety Concerns

Analysis of the preclinical, clinical and postmarketing data lead to the following important identified risks and important missing information:

Table 14 Summary of Ongoing Safety Concerns

Important identified risks	Hypersensitivity Injection site reactions
Important potential risks	None identified
Important missing information	Patients with renal or hepatic impairment Pregnant and lactating women Women with a history of or current Type I hypersensitivity

2.0 PHARMACOVIGILANCE PLAN

2.1 Routine Pharmacovigilance Practices

Schering-Plough has standard practices for routine pharmacovigilance activities involving spontaneous postmarketing adverse event reports, serious adverse events from clinical studies, pregnancy exposures, lactation exposures, overdoses and medication errors. Routine pharmacovigilance includes systems and processes to ensure that information about all suspected adverse reactions reported to the company is collected, the preparation of reports for regulatory authorities is made, and continuous monitoring of the safety profile of approved products.

2.2 Summary of Safety Concern and Planned Pharmacovigilance Actions

Routine pharmacovigilance will be carried out for the important identified risks and the important missing information (**Table 15**).

Table 15 Summary of Safety Concern and Planned Pharmacovigilance Actions

Safety Concern	Planned Action(s)
Important identified risks: Hypersensitivity Injection site reactions	Routine pharmacovigilance activities
Important potential risks: None identified	Not applicable
Important missing information: Patients with renal or hepatic impairment Pregnant and lactating women Women with a history of or current Type I hypersensitivity	Routine pharmacovigilance activities

2.3 Detailed Action Plan for Specific Safety Concerns

Tables 16, 17, 18, 19, 20, and **21** provide a detailed action plan for each of the specified adverse events/adverse reactions of concern with use of ganirelix.

Table 16 Detailed Action Plan for Specific Safety Concerns

Safety concern	Hypersensitivity
Action(s) proposed	Routine pharmacovigilance activities with close surveillance including safety signaling review
Objective of proposed action(s)	To determine changes in the severity and frequency. To identify potential safety signals.
Rationale for proposed action(s)	As these events are rare, case review is the appropriate manner to monitor for potential changes in the nature, frequency, severity, and other characteristics of the reported events.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	The EU SPC and CCDS will be updated as needed.
Milestones for evaluation and reporting including justification for choice of milestones	Ongoing. Including periodic review with updates in the EU SPC and CCDS as needed.
Titles of protocols	Not applicable

Abbreviations: CCDS = Company Core Data Sheet; EU = European Union; SPC = Summary of Product Characteristics

Table 17 Detailed Action Plan for Specific Safety Concerns

Safety concern	Injection site reactions
Action(s) proposed	Routine pharmacovigilance activities with close surveillance including safety signaling review
Objective of proposed action(s)	To determine changes in the severity and frequency. To identify potential safety signals.
Rationale for proposed action(s)	As these events are rare, case review is the appropriate manner to monitor for potential changes in the nature, frequency, severity, and other characteristics of the reported events.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	The EU SPC and CCDS will be updated as needed.
Milestones for evaluation and reporting including justification for choice of milestones	Ongoing. Including periodic review with updates in the EU SPC and CCDS as needed.
Titles of protocols	Not applicable

Abbreviations: CCDS = Company Core Data Sheet; EU = European Union; SPC = Summary of Product Characteristics

Table 18 Detailed Action Plan for Specific Safety Concerns

Safety concern	Patients with renal or hepatic impairment
Action(s) proposed	Routine pharmacovigilance activities with close surveillance including safety signaling review
Objective of proposed action(s)	To identify potential safety signals
Rationale for proposed action(s)	The target population consists of patients with an indication for controlled ovarian stimulation prior to IVF or ICSI and otherwise healthy. It is very unlikely that a patient with moderate or severe renal or hepatic impairment would undergo ART treatment.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	The EU SPC and CCDS will be updated as needed.
Milestones for evaluation and reporting including justification for choice of milestones	Ongoing. Including periodic review with updates in the EU SPC and CCDS as needed.
Titles of protocols	Not applicable.

Abbreviations: ART = assisted reproductive technology; CCDS = Company Core Data Sheet; EU = European Union; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; SPC = Summary of Product Characteristics

Table 19 Detailed Action Plan for Specific Safety Concerns

Safety concern	Pregnant and lactating women
Action(s) proposed	Routine pharmacovigilance activities with close surveillance including safety signaling review
Objective of proposed action(s)	To identify potential safety signals
Rationale for proposed action(s)	Case review is the appropriate manner to monitor for pregnant and/or lactating patients who inadvertently started ART treatment, as this is very unlikely.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	The EU SPC and CCDS will be updated as needed.
Milestones for evaluation and reporting including justification for choice of milestones	Ongoing. Including periodic review with updates in the EU SPC and CCDS as needed.
Titles of protocols	Not applicable.

Abbreviations: ART = assisted reproductive technology; EU = European Union; CCDS = Company Core Data Sheet; SPC = Summary of Product Characteristics

Table 20 Detailed Action Plan for Specific Safety Concerns

Safety concern	Women with a history of or current type I hypersensitivity
Action(s) proposed	Routine pharmacovigilance activities with close surveillance including safety signaling review
Objective of proposed action(s)	To identify potential safety signals
Rationale for proposed action(s)	Case review is the appropriate manner to monitor for potential changes in the nature, frequency, severity, and other characteristics of the reported events.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	The EU SPC and CCDS will be updated as needed.
Milestones for evaluation and reporting including justification for choice of milestones	Ongoing. Including periodic review with updates in the EU SPC and CCDS as needed.
Titles of protocols	Not applicable.

Abbreviations: CCDS = Company Core Data Sheet; EU = European Union; SPC = Summary of Product Characteristics

Table 21 Detailed Action Plan for Specific Safety Concerns

Safety concern	ART-related events
Action(s) proposed	Routine pharmacovigilance activities with close surveillance including safety signaling review
Objective of proposed action(s)	To determine changes in the severity and frequency. To identify potential safety signals.
Rationale for proposed action(s)	Case review is the appropriate manner to monitor for potential changes in the nature, frequency, severity, and other characteristics of the reported events.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	The EU SPC and CCDS will be updated as needed.
Milestones for evaluation and reporting including justification for choice of milestones	Ongoing. Including periodic review with updates in the EU SPC and CCDS as needed.
Titles of protocols	Not applicable

2.4 Overview of Study Protocols for the Pharmacovigilance Plan

No studies have been planned for the pharmacovigilance plan.

2.5 RMP Updates

- Injection site reactions are included as an important identified risk separate from Hypersensitivity and the postmarketing data for both risks have been updated.
- Nonclinical data has been added to the RMP.
- A statement regarding cumulative regulatory actions taken has been included in the RMP.
- Postmarketing data has been added to the ART-related related events and Use of Ganirelix During Pregnancy or Lactation (**Section 1.9.4**).
- **Section 1.9.4**, Potential for Off-label use has been updated to include Use in Male Patients.
- A detailed action plan for ART-related risks has been added to the RMP.

2.6 Summary of Outstanding Actions, Including Milestones

As routine pharmacovigilance is considered to be sufficient for the important identified risks and the important missing information, this section is not applicable.

PART II

3.0 EVALUATION OF THE NEED FOR RISK MINIMIZATION ACTIVITIES

3.1 Summary of Planned Actions for Important Safety Concerns

A summary of planned actions for important safety concerns is provided in **Table 22**.

Table 22 Summary of Planned Actions for Identified Safety Concerns

Safety Concern	Routine Risk Minimization Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
Important identified risk:		
Hypersensitivity	Yes	The following undesirable effects are included in the EU SPC Section 4.8 (Undesirable effects): Immune system disorders. Very rarely cases of hypersensitivity reactions including various symptoms such as rash, facial swelling and dyspnoea have been reported among patients administered Orgalutran with FSH. The following warnings and precautions are included in the EU SPC Section 4.4 (Special warnings and precautions for use): ▪ Special care should be taken in women with signs and symptoms of active allergic conditions. In the absence of clinical experience, Orgalutran treatment is not advised in women with severe allergic conditions. In addition, the following contraindications are included in the EU SPC Section 4.3 (Contraindications): ▪ Hypersensitivity to the active substance or to any of the excipients. ▪ Hypersensitivity GnRH or any other GnRH analogue.
Injection site reactions	Yes	The following undesirable effects are included in the EU SPC Section 4.8 (Undesirable effects): *General disorders and administration site conditions.* ▪ Orgalutran may cause a local skin reaction at the site of injection (predominantly redness, with or without swelling). In clinical studies, one hour after injection, the

Table 22 Summary of Planned Actions for Identified Safety Concerns

		incidence of at least one moderate or severe local skin reaction per treatment cycle, as reported by patients, was 12% in Orgalutran treated patients and 25% in patients treated subcutaneously with a GnRH agonist. The local reactions generally disappear within 4 hours after administration.
Important potential risks:	Not applicable	Not applicable
Important missing information:		
Patients with renal or hepatic impairment Pregnant and lactating women	Yes Yes	The following contraindications are included in the EU SPC Section 4.3 (Contraindications): • Moderate or severe impairment of renal or hepatic function.The following contraindications are included in the EU SPC Section 4.3 (Contraindications): ▪ Pregnancy or lactation. The following text is included in the EU SPC Section 4.6 (Pregnancy and lactation): ▪ No clinical data on exposed pregnancies are available. ▪ In animals, exposure to ganirelix at the time of implantation resulted in litter resorption (see 5.3 Preclinical safety data). The relevance of these data for humans is unknown. ▪ It is not known whether ganirelix is excreted in breast milk. ▪ The use of ganirelix is contraindicated during pregnancy and lactation. (see Section 4.3 Contraindications). In the EU SPC Section 5.3 (Preclinical safety data) the following information is included: 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.
Women with a history of or current Type I hypersensitivity	Yes	Refer to hypersensitivity

Abbreviations: GnRH = gonadotropin-releasing hormone; EU = European Union; SPC = Summary of Product

Characteristics

3.2 Potential for Medication Errors

The potential for any medication errors is regularly reviewed by the MAH. The review includes potential errors resulting from naming, presentation, instructions for use (e.g., regarding reconstitution, parenteral routes of administration, and dose calculation), labeling, and accidental exposure in children. No new safety concerns regarding medication errors have been identified. The MAH will continue to monitor reports of medication errors.

4.0 RISK MINIMIZATION PLAN

Routine risk minimization activities are adequate and no additional activities are proposed.

5.0 SUMMARY OF THE RISK MANAGEMENT PLAN

Table 23 provides a summary of the RMP for ganirelix.

Table 23 Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
Important identified risk:		
Hypersensitivity	Routine PV • Routine PV activity with close surveillance including safety signaling review	Routine Risk Minimization • contraindication in Section 4.3 of the EU SPC • Listed as a reported undesirable reaction in Section 4.8 of the EU SPC.
Injection site reactions	Routine PV • Routine PV activity with close surveillance including safety signaling review	Routine Risk Minimization • Listed as a reported undesirable reaction in Section 4.8 of the EU SPC.
Important potential risks: None		

Table 23 Summary of the Risk Management Plan

Important missing information		
Patients with renal or hepatic impairment	Routine PV • Routine PV activity with close surveillance including safety signaling review	Routine Risk Minimization • contraindication in Section 4.3 of the EU SPC for patients with moderate or severe renal or hepatic impairment.
Pregnant and lactating women	Routine PV • Routine PV activity with close surveillance including safety signaling review	Routine Risk Minimization • contraindication in Section 4.3 of the EU SPC • warning in Section 4.6 of the EU SPC that there are no adequate data from the use of ganirelix in pregnant women. It is not known whether ganirelix is excreted in breast milk. The use of ganirelix is contraindication during pregnancy and lactation.
Women with a history of or current type hypersensitivity	Routine PV • Routine PV activity with close surveillance including safety signaling review	Routine Risk Minimization • contraindication in Section 4.3 of the EU SPC • warning in Section 4.4 of the EU SPC that special care should be taken in women with signs and symptoms of active allergic conditions. In the absence of clinical experience, ganirelix treatment is not advised in women with severe allergic conditions.

CCDS = Company Core Data Sheet; EU = European Union; PV = pharmacovigilance; SPC = Summary of Product Characteristics

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Annex 4

Synopsis of Ongoing and Completed Pharmacoepidemiological Study Program

Not applicable

Annex 6

Newly Available Study Reports

Not applicable