

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Ganirelix SUN 0.25 mg/0.5 ml
solution for injection in pre-filled syringe
Sun Pharmaceutical Industries Europe B.V., the Netherlands**

ganirelix (as acetate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2644/001/DC
Registration number in the Netherlands: RVG 111978**

10 July 2013

Pharmacotherapeutic group:	pituitary and hypothalamic hormones and analogues, anti-gonadotrophin releasing hormones
ATC code:	H01CC01
Route of administration:	subcutaneous
Therapeutic indication:	prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART).
Prescription status:	prescription only
Date of authorisation in NL:	4 July 2013
Concerned Member States:	Decentralised procedure with AT, DE, DK, ES, FI, FR, IT, NO, SE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ganirelix SUN 0.25 mg/0.5 ml solution for injection in pre-filled syringe from Sun Pharmaceutical Industries Europe B.V. The date of authorisation was on 4 July 2013 in the Netherlands.

The product is indicated for the prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART). In clinical studies ganirelix was used with recombinant human follicle stimulating hormone (FSH) or corifollitropin alfa, the sustained follicle stimulant.

A comprehensive description of the indications and posology is given in the SPC.

Ganirelix is a GnRH antagonist, which modulates the hypothalamic-pituitary-gonadal axis by competitive binding to the GnRH receptors in the pituitary gland. As a result a rapid, profound, reversible suppression of endogenous gonadotrophins occurs, without initial stimulation as induced by GnRH agonists. Following administration of multiple doses of 0.25 mg ganirelix to female volunteers serum LH, FSH and E2 concentrations were maximally decreased by 74 %, 32 % and 25 % at 4, 16 and 16 hours after injection, respectively. Serum hormone levels returned to pre-treatment values within two days after the last injection.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Orgalutran 0.25 mg/0.5 ml solution for injection which has been registered in the EEA by N.V. Organon since 17 May 2000 (original product), with EU license number EU/1/00/130/001-002.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Ganirelix SUN 0.25 mg/0.5 ml solution for injection in pre-filled syringe is an aqueous solution for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is ganirelix acetate, an established active substance not described in any pharmacopoeia. It is a white to off white powder, which is soluble in water. The substance is a synthetic decapeptide, is hygroscopic and contains ten chiral centres.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Synthesis of the synthetic peptide consists of attachment synthesis of several building blocks. The specifications of the starting materials are acceptable. The residual solvents and other reagents have been adequately discussed. Validation reports and descriptions of analytical procedures have been provided.

Quality control of drug substance

The drug substance specification has been established in-house and contains appropriate tests. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three production-scale batches stored at $5 \pm 3^\circ\text{C}$ (two batches up to 12 months and one up to 9 months) and $25^\circ\text{C}/60\% \text{ RH}$ (up to 6 months). Based on the results, a re-test period of 1 year when stored at $2-8^\circ\text{C}$ is acceptable.

Medicinal Product

Composition

Ganirelix SUN 0.25 mg/0.5 ml is a clear and colourless aqueous solution with a pH between 4.5 to 5.5 and an osmolality between 250 to 350 mOsm/kg.

The solution is packed in pre-filled syringes, each containing 0.25 mg of ganirelix (as acetate) in 0.5 ml aqueous solution.

The syringes are made of colourless type I glass containing 0.5 ml of sterile, ready for use, aqueous solution closed with a grey rubber plunger stopper and polypropylene plunger rod. Injection needles (27 G) are affixed to the barrel and provided with grey elastomeric needle shield and polypropylene rigid needle shield.

The excipients are: glacial acetic acid (E260), mannitol (E421, water for injections. Sodium hydroxide and glacial acetic acid may be used for pH adjustment.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. To achieve this goal the MAH has chosen the same excipients as the innovator. The main development studies performed were compatibility studies and container closure system studies. A batch of the generic product was compared to a batch of the innovator with respect to appearance, assay, related substances, pH, absorbance, transmittance and osmolality. No significant differences were observed. The MAH adequately demonstrated equivalence with respect to chemical-pharmaceutical properties. The selected terminal sterilisation method is in line with the Ph.Eur. and therefore acceptable. No drug substance overage is included in the drug product, since no reduction of the drug substance was observed during the manufacturing process. An overfill of 0.02 ml is used in the drug product to compensate for the amount of solution which remains in the container closure system. The overfill is acceptable, since the drug product complies with the requirements for extractable volume of the Ph.Eur. at release. The pharmaceutical development of the product has been adequately performed.

Microbiological attributes

The drug product contains no antimicrobial preservative. Container closure integrity was tested by testing sterility according to the Ph.Eur. in the final primary packaging and by microbial challenge testing. Based on the results it was concluded that the container closure system adequately protects the drug product.

Manufacturing process

The manufacturing of the drug product comprises of preparation of the bulk solution, filtration, filling, terminal sterilisation and packaging. Satisfactory process validation data on the product has been provided for three full-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification of ganirelix and mannitol, pH, extractable volume, volume variation, absorbance, transmittance, osmolality, particulate matter, bacterial endotoxins, sterility, related substances and assay of ganirelix and mannitol.

The release and shelf-life limits are identical, with the exception of one impurity. The stability indicating nature of the method used for assay and related substances of ganirelix has been adequately demonstrated. All analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided of three full-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed marketing package in horizontal position. The same trends were observed in related substances at both conditions. The trends were more pronounced at accelerated conditions. All results remained well within the specification limits.

All other parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits. Photostability stability studies were performed on one batch in the primary packaging. No changes were observed.

Based on the results of the stability data provided, a shelf life of 24 months without special storage conditions was granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Orgalutran, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ganirelix released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ganirelix is a well-known active substance with established efficacy and tolerability when administered subcutaneously.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

The composition of Ganirelix SUN 0.25 mg/0.5 ml is identical to the brand leader Orgalutran 0.25 mg/0.5 ml solution for injection (Merck Sharp & Dohme Limited). It contains the same active substance in the same concentration as the innovator product. According to the CPMP guideline "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev. 1), there is no requirement for a bioequivalence study for solutions for subcutaneous administration in case the generic formulations contains the same active substance in the same concentration as the reference product and the same excipients in similar amounts as the reference product. The MAH demonstrated that the excipients have no impact on the viscosity of the solution. The generic product and the reference product contain both acetic acid and mannitol as excipients. Both products have the same pH and osmolality (277 mosm/kg). Therefore it can be concluded that the amount of substances that influence the viscosity and the distribution in the injection site, will be similar. The lack of an *in vivo* bioequivalence study is considered acceptable.

Risk management plan

Ganirelix was first approved in 2000, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ganirelix can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Orgalutran.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. There were 14 questions addressing the key safety messages and two questions concerning the presentation of information. The questions cover the key safety messages, which are: indications, contra-

indications and warnings, treatment regimen, how to administer the injections, side effects, and storing the injections.

A number of people were unable or had difficulties with finding the answer to some of the questions. Although the user test did not pass the formal, predefined criteria (a satisfactory test outcome for the method outlined above is when 90% of literate adults are able to find the information requested within the leaflet, of whom 90% can show that they understand it) the user test and PL are found to be acceptable, as it is in accordance with the innovator's. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ganirelix SUN 0.25 mg/0.5 ml solution for injection in pre-filled syringe has a proven chemical-pharmaceutical quality and is a generic form of Orgalutran 0.25 mg/0.5 ml solution for injection. Orgalutran 0.25 mg/0.5 ml is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for the same parenteral use (subcutaneous injection), no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ganirelix SUN 0.25 mg/0.5 ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 24 April 2013. Ganirelix SUN 0.25 mg/0.5 ml solution for injection in pre-filled syringe was authorised in the Netherlands on 4 July 2013.

The date for the first renewal will be: 24 April 2018.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the on-going long term studies of the drug product up to 36 months.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
COH	Controlled Ovarian Hyperstimulation
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
LH	Luteinising Hormone
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached