COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cetrorelix Sun 0.25 mg solution for injection in a pre-filled syringe

(cetrorelix)

NL/H/5023/001/DC

Date: 25 February 2021

This module reflects the scientific discussion for the approval of Cetrorelix Sun 0.25 mg solution for injection in a pre-filled syringe. The procedure was finalised at 19 November 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cetrorelix Sun 0.25 mg solution for injection in a pre-filled syringe, from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.
In clinical trials cetrorelix was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle-stimulating hormone (FSH) suggested similar efficacy.
A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Cetrotide 0.25 mg, powder for solution for injection which has been registered in the EEA by Merck Europe B.V. since 13 April 1999 via a centralised procedure (EU/1/99/100).

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, as the pharmaceutical form of the innovator product Cetrotide (powder for solution for injection) is different than the pharmaceutical form of Cetrorelix Sun (solution for injection in a pre-filled syringe).

II. QUALITY ASPECTS

II.1 Introduction

Cetrorelix Sun is a clear, colourless solution free from visible particles with a pH from 4.0-6.0. Each pre-filled syringe of 1 ml solution contains 0.25 mg cetrorelix (as acetate).

The pre-filled syringe presentation consists of type I clear glass barrel (1 ml) affixed with a 27 G ½ inch needle and stoppered with a bromobutyl elastomer plunger stopper. The syringe has a white plunger rod and an automatic safety system.

One or 7 pre-filled syringe(s) assembled with safety devices are packed in 1 or 7 blister(s). One or 7 blister(s) along with 1 or 7 alcohol swabs will be packed in a carton.

The excipients are: mannitol (E421), S-lactic acid and water for injection.

II.2 Drug Substance

The active substance is cetrorelix, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off white amorphous, hygroscopic powder, sparingly soluble in water. Cetrorelix is a 10 amino acid peptide and contains 10 chiral centres, one for each amino acid (5 D-amino acids and 5 L-amino acids). The stereochemistry is controlled by specific optical rotation.

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 MAH 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

The manufacturing process of cetrorelix acetate is a typical solid phase peptide synthesis where multiple amino acids are linked via amide bonds in a pre-defined sequence The process consists has been sufficiently described. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification by the finished product manufacturer is identical to that of the ASMF holder, without any additional requirements. 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 full scaled batches by the drug substance manufacturer and for two full scaled batches by the finished product manufacturer.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 2-8°C (12 months) and 25°C/60% RH (6 months). The stability data showed no clear trends or changes in any of the tested parameters at both storage conditions and all parameters complied with the specifications. Results of a photostability test as per ICH Q1B showed that the drug substance is not sensitive to light. A retest period of 18 months and storage condition 'Preserve in tight, light-resistant container at temperature between 2-8°C' is supported by the stability data.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The drug product differs in formulation from the reference medicinal product. The reference medicinal product is a powder and solvent for solution for injection that needs to be reconstituted with the water for injections supplied in a 1 ml pre-filled syringe.

The development was guided by risk assessments to identify the critical drug substance attributes, critical material attributes and critical process parameters. To mitigate the identified risks an adequate control strategy was implemented. The main formulation development studies were the characterisation of the reference product and physicochemical comparison with the test products. The composition of the test product differs from that of the reference product with respect to the excipient lactic acid that is added to the test product for pH adjustment and is not present in the reference product. It has been sufficiently demonstrated that the difference in excipients between the test and reference product has no impact on physico-chemical properties, particularly viscosity. Based on the results of the *in-vitro* comparison the absence of bioequivalence studies was justified. The main manufacturing process development studies were the optimisation of preparation of the bulk solution, compatibility studies with manufacturing equipment and selection of the sterilisation method. The drug product is sterilised by sterile filtration into pre-sterilised primary packaging components. The choice for sterile filtration is justified as significant degradation was seen under terminal sterilisation conditions in an autoclave. The pharmaceutical development has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are the preparation of the bulk solution, aseptic filtration, aseptic filtration and filling and stoppering of the pre-filled syringes. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines.

Control of excipients

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

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, pH, osmolality, extractable volume, particulate contamination, sterility, bacterial endotoxins, related substances, assay, mannitol content, glide force, break-loose force, uniformity of dosage units, weight per ml and viscosity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three scaled

batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches stored at 2-8°C (6 months) and 25°C/60% RH (12 months). The conditions used in the stability studies are according to the ICH stability guideline. An additional pilot scale batch was stored only at 30°C/65% RH (3 months). Provided stability data fully support the claimed shelf-life of 2 years for the product when stored in a refrigerator at 2-8°C. The claim in the SmPC that 'The unopened product may be stored in the original package at room temperature (not above 25°C) for up to three months' is supported by the formal stability studies at accelerated conditions (25°C/60% RH).

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cetrorelix Sun has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cetrorelix Sun is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Cetrotide which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cetrorelix is a well-known active substance with established efficacy and tolerability. 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.

IV.2 Pharmacokinetics

Biowaiver

The applied for product has a different dosage form compared to the reference product (solution/lyophilized powder). The MAH applies for the waiver of any bioequivalence studies and this is agreed. Both the test and the reference product are considered to be a simple aqueous solution at the moment of administration. In line with the Note or Guidance on the investigation of Bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), bioequivalence studies are not considered necessary. Further, the addition of lactic acid is not expected to influence local absorption to a clinically relevant extent. Therefore, it can safely be assumed that the Cetrorelix SUN and Cetrotide products demonstrate comparable bioavailability and it is agreed with the MAH that no bioequivalence study is performed.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cetrorelix Sun.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Systemic allergic/pseudo-allergic reactions (including e.g. anaphylaxis) • OHSS in connection to the COS procedure
Important potential risks	• Congenital anomalies
Missing information	• Infertile premenopausal women with PCOS • Infertile premenopausal women more than 40 years old • Infertile premenopausal women with corpus luteum insufficiency • Infertile premenopausal women with liver and/or renal impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cetrotide. No new clinical studies were conducted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 a pilot test followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cetrorelix Sun 0.25 mg solution for injection in a pre-filled syringe has a proven chemical-pharmaceutical quality and is a hybrid form of Cetrotide 0.25 mg, powder for solution for injection. Cetrotide is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

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 Cetrorelix Sun with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 November 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse