COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Fulvestrant Sun 250 mg solution for injection in pre-filled syringe

# (fulvestrant)

# NL/H/3953/001/DC

# Date: 13 November 2018

**This module reflects the scientific discussion for the approval of Fulvestrant Sun. The procedure was finalised at 29 March 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
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| ASMF | Active Substance Master File |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| 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 Fulvestrant Sun 250 mg solution for injection in pre-filled syringe from Sun Pharmaceutical Industries Europe B.V.

The product is indicated:

- as monotherapy for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:
    - not previously treated with endocrine therapy, or
    - with disease relapse on or after adjuvant antiestrogen therapy, or disease progression on antiestrogen therapy.

- in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy (see SmPC section 5.1).

In pre- or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Faslodex 250 mg solution for injection (NL License RVG 71834) which has been registered in the EU by Astra Zeneca UK Ltd since March 2004 (original product).

The concerned member states (CMS) involved in this procedure were Germany, Spain, France, Italy, Poland, Romania, Sweden and United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1).

# II. QUALITY ASPECTS

## II.1 Introduction

Fulvestrant Sun is a clear colourless to yellow viscous solution for injection free from visible particles, in a pre-filled syringe. Each ml of the solution contains 50 mg fulvestrant.

The pre-filled syringe presentation consists of:

- One clear type 1 glass pre-filled syringe with polystyrene plunger rod and elastomeric plunger stopper, fitted with a Plastic Rigid Tip cap, containing 5 ml fulvestrant solution

for injection. A safety needle (BD SafetyGlide) for connection to the barrel is also provided.

- Two clear type 1 glass pre-filled syringes with polystyrene plunger rod and elastomeric plunger stopper, fitted with a Plastic Rigid Tip cap, each containing 5 ml fulvestrant solution for injection. Two safety needles (BD SafetyGlide) for connection to each barrel are also provided.

The excipients are ethanol (96%), benzyl alcohol (E1519) benzyl benzoate and refined castor oil.

## II.2 Drug Substance

The active substance is fulvestrant, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder and is practically insoluble in water. It contains six asymmetric carbon atoms and a stereogenic sulphoxide in the side chain. The active ingredient is a mixture of two diastereoisomers: fulvestrant sulphoxide A and B, having the same absolute configuration at each of the stereogenic centres in the steroid system, but different absolute configurations at the sulphur atom.

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

Fulvestrant is synthesised in two steps followed by purification. The active substance is adequately characterised. The starting materials are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. It meets the requirements of the monograph in the Ph.Eur. and includes additional requirement for residual solvents, microbial purity, colour index and clarity. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 12 months/years. Based on the data submitted, a retest period could be granted of 18 months when stored at 2-8°C.

## 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 composition is qualitatively and quantitatively the same as for the reference product. The sterilisation method of the empty syringes has been adequately justified. Pharmaceutical development has been adequately described.

Manufacturing process

The manufacturing process is a non-standard manufacturing process, consisting of preparation of the solution, sterile filtration, filling and stoppering. No sterilisation in the final container is performed. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented three batches in accordance with the relevant European guidelines.

Control of excipients

All excipients are of Ph.Eur. quality. 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, identification, extractable volume, water content, viscosity, colour and clarity of the solution, free fatty acids, particulate matter, uniformity of dosage units, related substances, sterility and bacterial endotoxin test (BET), assay for fulvestrant, benzyl alcohol, benzyl benzoate, ethanol, glide force, break-loose force and density. 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 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability studies at accelerated (25°C/60% RH, six months) and long-term (2-8°C) conditions are performed on three batches. The conditions are according to the ICH stability guideline. 12 months data are available. The proposed shelf-life of two years with storage conditions 2-8°C, store in original packaging in order to protect from light for the drug product is supported by the stability data.
A photostability study was performed, in accordance with ICH Q1 guidelines. The results of this photostability study demonstrate that light has no impact on the quality of the drug product. However, based on development data and the SmPC of the reference product, the MAH proposed to store the medicinal product protected from light. As during development, photostability and tenability studies show that the drug product should be stored protected from light, the proposal to store the medicinal product protected from light is considered appropriate.

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 Fulvestrant 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 Fulvestrant Sun is intended for generic 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 generic formulation of Faslodex 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

Fulvestrant 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

Fulvestrant Sun 250 mg solution for injection in pre-filled syringe is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Fulvestrant Sun is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

## 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 Fulvestrant Sun.

**Table 2. Summary table of safety concerns as approved in RMP**

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| Important identified risks | • Injection site reactions<br>• Increased risk of bleeding at the injection site<br>• Venous thromboembolic events<br>• Hypersensitivity reactions<br>• Hepatobiliary disorders |
| Important potential risks | • Reduced bone mineral density (osteopenia) and osteoporosis<br>• Reprotoxicity<br>• Pulmonary microembolism of oily solutions<br>• Ischaemic cardiovascular events<br>• Endometrial dysplasia<br>• Interstitial lung disease<br>• Vasculitis |
| Missing information | • Use in children and adolescents<br>• Use in patients with severe hepatic impairments<br>• Use in patients with severe renal impairments |

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 Faslodex. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic 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. 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 PL of medicinal products for human use.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fulvestrant Sun 250 mg solution for injection in pre-filled syringe has a proven chemical-pharmaceutical quality and is a generic form of Faslodex 250 mg solution for injection. Faslodex is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of in vitro studies on the relevant quality attributes. 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 Fulvestrant Sun with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 March 2018.

## 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 |
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