COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fulvefar 250 mg solution for injection in pre-filled syringe

(fulvestrant)

NL/H/4908/001/DC

Date: 28 September 2020

This module reflects the scientific discussion for the approval of Fulvefar. The procedure was finalised at 12 August 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
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 Fulvefar 250 mg solution for injection in pre-filled syringe from Laboratorios Farmalán, S.A.

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 EEA by Astra Zeneca UK Ltd since March 2004.

The concerned member states (CMS) involved in this procedure were Austria, Czech Republic, Hungary, Poland and the Slovak Republic.

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

II. QUALITY ASPECTS

II.1 Introduction

Fulvefar 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.
- Six 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. Six 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 insoluble in water. The drug substance corresponds to a mixture of two epimers. Polymorphism is not relevant as the drug substance is dissolved during the manufacturing process of the drug product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP with additional requirements for identification, residual solvents and microbial enumeration. Batch analytical data demonstrating compliance with this specification have been provided for four commercial scale batches.

Stability of drug substance

Stability data on the active substance have been provided for ten pilot and commercial scale drug substance batches stored at 5 ± 3°C (between 0 and 60 months) and 25°C/60% RH

(between 0 and 6 months). Based on the data submitted, a retest period could be granted of five years when stored under the stated conditions.

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. Formulation development studies included solubility studies, order of addition, compatibility with equipment, stability studies, and filter validation studies. 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 bulk solution, pre-filtration, sterile filtration, filling under aseptic conditions. The sterilisation processes of the primary packaging have been sufficiently described. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented three full scale batches in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with the respective current Ph.Eur. monograph. 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, water content, viscosity, relative density, degree of colouration, uniformity of content by mass variation, assay of fulvestrant, excipient content, free fatty acid, related substances, visible particles, sub-visible particles, extractable volume, break loose force, gliding force, bacterial endotoxins, and sterility. 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 commercial scale 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 full scale batches stored at 2-8°C (18 months) and 25°C/60% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the same container closure system which will be used for commercial batches (glass barrel, elastomeric tip cap, elastomeric plunger stopper, plastic plunger rod, and a plastic backstop) in horizontal and upright position. No out of specification results have been observed. Photostability studies

were performed in accordance with ICH recommendations and showed that the product is stable in the primary packaging when exposed to light. The claimed storage conditions 'Store and transport refrigerated (2°C-8°C). Store the pre-filled syringe in the original package in order to protect from light.' are in line with those of the reference product and are acceptable, even though protection from light would strictly speaking not be needed.

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 Fulvefar 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 Fulvefar 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

Fulvefar 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 Fulvefar 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 Fulvefar.

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

Important identified risks	• Injection site reactions • Increased risk of bleeding at the injection site • Venous thromboembolic events • Hypersensitivity reactions • Hepatobiliary disorders
Important potential risks	• Reduced bone mineral density (osteopenia) and osteoporosis • Ischaemic cardiovascular events • Endometrial dysplasia • Interstitial lung disease • Vasculitis • Pulmonary microembolism of oily solutions • Reprotoxicity (fertility, pregnancy and lactation)

Missing information	• Paediatric use • Use in patients with severe hepatic impairments • 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 with two participants, followed by two rounds with ten 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fulvefar 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.

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 Fulvefar with the reference

product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 August 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