COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fulvestrant Eugia 250 mg, solution for injection in pre-filled syringe (fulvestrant)

NL/H/5388/001/DC

Date: 6 January 2023

This module reflects the scientific discussion for the approval of Fulvestrant Eugia 250 mg, solution for injection in pre-filled syringe. The procedure was finalised at 14 September 2022. 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 medicinal 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 Eugia 250 mg, solution for injection in pre-filled syringe, from Eugia Pharma (Malta) Limited.

The product is indicated:

- as monotherapy for the treatment of oestrogen 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 antioestrogen therapy, or disease progression on antioestrogen 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 the SmPC section 5.1).

In pre- or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinising 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, authorised in the EEA by AstraZeneca on 10 March 2004 (EU/1/03/269/001-002).

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Fulvestrant Eugia is a pre-filled syringe with a clear, colourless to yellow viscous solution essentially free from visible particles. One syringe contains as active substance 250 mg fulvestrant in 5 mL of solution (50 mg/mL).

The solution is packaged in a 5 mL type-I clear glass barrel with OVS tip cap and stoppered with a grey plunger with a bromobutyl rubber stopper, along with a plunger rod. A safety glide hypodermic needle for connection to the barrel is provided in the packaging to administer the fulvestrant solution for injection. The glass syringe barrel along with the needle are placed in a protective plastic tray with transparent lid.

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

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, insoluble in water. The drug substance exists of a mixture of two epimers. Polymorphism is not relevant as the drug substance is dissolved during manufacturing 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 of the CEP, with additional requirements for residual solvents conform the CEP and microbiological purity. The proposed acceptance criterion for the bacterial endotoxins test is more tight than the acceptance criterion of the Ph.Eur. 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 commercial scale batches.

Stability of drug substance

The CEP did not claim a retest period. Stability data on the active substance have been provided for seven pilot scale batches and three full scale batches in accordance with applicable European guidelines. No significant changes or specific trends have been observed at both storage conditions (at 5°C ± 3°C and at 25°C/60% RH). Based on the data submitted, a retest period could be granted of 60 months when stored at 5°C ± 3°C.

II.3 Medicinal Product

Pharmaceutical development

The aim of the development is to develop a product similar to the reference product. 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 pharmaceutical development of the product has been adequately performed by establishment of the quality target product profile and risk assessments for the critical quality attributes of the drug product. A bioequivalence study is not required because the new product is of same type of oily solution, contains the same concentration of the same active substance, and the same excipients in similar amounts as the reference product and the viscosity of the test and reference product is comparable.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The process includes preparation of the bulk solution, pre-filtration, sterilising filtration, filling and stoppering under aseptic conditions and labelling and packaging. The process is regarded as a non-standard process due to the aseptic processing steps. The primary packaging materials are purchased ready to use and sterile. Process validation data on the product has been presented for three full scale batches.

Control of excipients

The excipients comply with their respective Ph.Eur. monograph with additional controls for microbial quality and endotoxins where relevant. These specifications are acceptable.

Microbiological attributes

The glass barrels with OVS tip caps and the plunger stoppers are sterilised by ethylene oxide. The information provided on the sterilisation processes of the primary packaging material is considered sufficient. There was a break-out session discussion regarding validation of the ethylene oxide sterilisation process, which was resolved positively by the MAH before the end of the procedure.

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, assay, related substances, free fatty acid content, benzyl alcohol content, benzaldehyde content, particulate contamination, ethanol content, water content, viscosity, extractable volume, benzyl benzoate content, sterility, bacterial endotoxins test, appearance of solution and syringe functionality tests (break loose and glide force). The proposed release and shelf life limits are identical except for total impurities. The drug product specification is acceptable for adequate quality control. Suitable descriptions and validation data of analytical methods have been provided, where relevant.

Batch analytical data from three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

A complete risk evaluation for the presence of nitrosamines in the product was performed, considering information from the active substance, the excipients, the primary packaging materials and the manufacturing process and equipment of both the active substance and the drug product. Based on the assessed parameters, no risks have been identified. The risk evaluation concerning the presence of nitrosamine impurities is considered complete and adequate.

Stability of drug product

Stability data on the product have been provided for three full scaled batches stored at 2-8°C (24 months) and 25°C/60% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. At accelerated conditions, slight increasing trends were observed for one specific impurity, total impurities, benzaldehyde content, particulate contamination and viscosity. No clear trends were observed at long term conditions. All results at both conditions were well within the required limits. The proposed shelf life of 2 years when stored in a refrigerator (2-8°C) can be 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fulvestrant Eugia 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 Eugia 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 Eugia 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 intramuscular 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 Eugia is 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 Eugia.

Table 1. Summary of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Faslodex 250 mg solution for injection (EMEA/H/C/000540) for content and Mebeverine HCL Aurobindo 200 mg modified-release capsules, hard (NL/H/3750/001/DC) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fulvestrant Eugia 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 was deemed necessary.

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 Eugia with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 September 2022.

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
N/A	N/A	N/A	N/A	N/A	N/A