Public Assessment Report

Scientific discussion

Anidulafungine Teva 100 mg, powder for concentrate for solution for infusion

(anidulafungin)

NL/H/3836/001/DC

Date: 10 April 2018

This module reflects the scientific discussion for the approval of Anidulafungine Teva 100 mg, powder for concentrate for solution for infusion. The procedure was finalised on 17 January 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

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 Anidulafungine Teva 100 mg, powder for concentrate for solution for infusion, from Teva Nederland B.V.

The product is indicated for the treatment of invasive candidiasis in adult patients.

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 Ecalta 100 mg, powder for concentrate for solution for infusion (EU/1/07/416) which has been registered in the EEA by Pfizer Ltd since 27 July 2009 through a centralised procedure.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Denmark, Greece, Spain, Croatia, Hungary, Ireland, Italy, Luxembourg, Poland, Portugal, Romania, Sweden, Slovenia and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Anidulafungine Teva is a white to off-white powder for concentrate for solution for infusion, free of visible evidence of contamination. Each vial contains 100 mg anidulafungin. The reconstituted solution contains 3.33 mg/mL anidulafungin and the diluted solution contains 0.77 mg/mL anidulafungin. The reconstituted solution has a pH of 4.0 – 5.0.

The powder for concentrate for solution for infusion is packed in type 1 colourless glass vial, closed with type 1 butyl rubber stopper and aluminium metallic cap with polypropylene disk.

The excipients are: sucrose, polysorbate 80 (E433), tartaric acid, sodium hydroxide (E524) (for pH adjustment) and hydrochloric acid (E507) (for pH-adjustment).

II.2 Drug Substance

The active substance is anidulafungin, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Anidulafungin is a amorphous white or off-white powder and slightly soluble in methanol and practically insoluble in water or acetonitrile. It contains 15 chiral centres which are adequately controlled. The substance shows polymorphism and the amorphous form is used.

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

Anidulafungin is synthesised by a two stage fermentation process followed by chemical and purification step. The active substance is adequately characterised. The specifications for the staring materials and reagents are acceptable.

Quality control of drug substance
The active substance specification has been established in-house by the MAH and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 3 full scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 full scale batches at 5°C (6 months), -20°C (24 months) and -70°C (24 months) in accordance with applicable European guidelines. Based on the provided stability data the proposed retest period of 24 months and storage condition "in well closed container at temperature not exceeding -70°C and protected from light" are justified.

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 choices of the packaging and manufacturing process are justified in relation to the innovator, sterilisation by aseptic filtration is justified based on the lability of the active substance. The active substance is solubilised in micelles, which makes the drug product a complex formulation for which a biowaiver is requested. Therapeutic equivalence is demonstrated on basis of *in vitro* data such as micelle size, critical micelle concentration, maximum additive concentration, cloudy temperature, *in vitro* plasma binding, free fraction of active substance and *in vitro* drug release. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The drug product is manufactured according to a non-standard process; preparation of a bulk solution by mixing and dissolution of all ingredients, followed by aseptic filtration, filling, lyophilisation, capping and visual inspection and packaging. Process validation data on the product have been presented for 3 full scale 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 appearance, identity, uniformity of dosage units, water, assay, related substances, bacterial endotoxins and sterility as well as for the reconstituted solution and the final diluted product the reconstitution time, clarity, color, visible particles, sub-visible particles and pH. The release and shelf life acceptance limits are not identical for water and related substances. This is acceptable. 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 1 pilot and 3 full 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 1 pilot and 2 full scale batches stored at 2-8°C (3-6-9-12 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 proposed packaging. Photostability studies in accordance with ICH recommendations demonstrated that the product is stable when exposed to light. Under accelerated (i.e. 25°C/60% RH) conditions Impurity 1 increases from less than 0.1% to about 0.6%. Therefore, the proposed shelf-life of 18 months and storage condition of "Stored in a refrigerator (2°C to 8°C)" are justified. Stability data has been provided demonstrating that the product remains stable for 24 hours following reconstitution and for 48 hours following dilution, when stored at 15-25°C.

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 Anidulafungine Teva 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 Anidulafungine Teva 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 Ecalta 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

Anidulafungin 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

The MAH has compared the proposed drug product Anidulafungine Teva 100 mg, powder for concentrate for solution for infusion (Teva Nederland B.V., NL) with the reference product Ecalta 100 mg, powder for concentrate for solution for infusion (Pfizer Ltd, UK).

Because according to the MAH the reference composition containing fructose and mannitol is patented, the MAH has replaced them with sucrose. This difference in composition is acceptable.

Biowaiver
No clinical studies have been performed and none are required. According to the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr., 20 Jan 2010), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

According to the Guideline on Bioequivalence micelle formulations may be considered eligible for a biowaiver where:

a) rapid disassembly of the micelle on dilution occurs and the drug product is not designed to control release or disposition.
b) the method and rate of administration is the same as the currently approved product.
c) the excipients do not affect the disposition of the drug substance.

The following *in vitro* evaluations were carried out:

- Micelle size and distribution
- Critical Micelle Concentration (CMC)
- Maximum Additive Concentration (MAC)
- Free versus solubilised fractions of the active substance
- *In vitro* drug release from micelles
- *In vitro* protein binding

The data shows comparability between the reference and test product, however a concern was raised regarding the protein binding. Although based upon the free fraction equivalence could not be straight forward concluded, considering the similarity in composition between test and reference product, containing the same amount of polysorbate 80, a difference in rapid disassembly of the micelle on dilution is not expected and thus also not a difference in the free fraction. From a clinical point of view the application can be accepted.

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 Anidulafungine Teva.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Anaphylaxis and infusion-associated adverse events - Hepatobiliary adverse events
Important potential risks	- Convulsions - Anaesthetic exacerbation of infusion-associated adverse events - QT prolongation/torsade de pointes
Missing information	- Use in children/adolescents - Use in pregnant women - Use in elderly - Resistance

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 Ecalta No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is comparable 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 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 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet 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

Anidulafungine Teva 100 mg, powder for concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Ecalta 100 mg, powder for concentrate for solution for infusion. Ecalta 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 Anidulafungine Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 January 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