COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fosfomycine Midas 3000 mg, powder for oral solution

(fosfomycin trometamol)

NL/H/4186/001/DC

Date: 4 April 2019

This module reflects the scientific discussion for the approval of Fosfomycine Midas 3000 mg, powder for oral solution. The procedure was finalised at 12 December 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 Fosfomycine Midas 3000 mg, powder for oral solution, from Midas Pharma GmbH.

The product is indicated in the treatment of acute uncomplicated lower urinary tract infections in adult and adolescent females from 12 years of age.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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 Monuril 3000, granules for oral solution 3g (NL License RVG 13066) which has been registered in The Netherlands by Zambon Nederland B.V. since 29 March 1990.

The concerned member states (CMS) involved in this procedure were Germany, Denmark, Estonia, Finland, Lithuania, Latvia, Norway, Poland, Romania, Sweden and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Fosfomycine Midas is a white or off-white powder with orange flavour. Each sachet contains 5.631 g of fosfomycin trometamol, equivalent to 3 g of fosfomycin.

The powder for oral solution is packed in packed in paper/polyethylene/aluminium/polyethylene sachets. Each sachet contains 8.0 g of powder.

The excipients are: sucrose (E474), saccharin sodium (E954) and orange flavour (contains ethyl butyrate, linalool, arabic um (E414), dextrose monohydrate, maltodextrine, BHA (E320), ethyl hexanoate, isoamyl hexanoate, natural citral, isoamyl acetate, nerol, natural orange essential oil and natural lemon essential oil)

II.2 Drug Substance

The active substance is fosfomycin trometamol, an established active substance described in the European Pharmacopoeia. The active substance is white or almost white powder, very soluble in water and very hygroscopic. The structure of fosfomycin includes 2 stereogenic centres and has the 2R, 3S configuration. No polymorphism is described for fosfomycin trometamol, but it was demonstrated that the substance is consistently manufactured having the same solid state form. The active substance is the same as used in the reference product.

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

The manufacturing process comprises six chemical reaction steps followed by a purification step for the preparation of the key intermediate. No class 1 organic solvents are used in the process The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is in line with the Ph.Eur., with additional requirements for residual solvents in accordance with the specification from the active substance manufacturer, microbiological quality and particle size. 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.

Stability of drug substance

Stability data on the active substance have been provided for ten full scaled batches stored at 25°C/60% RH (6-24 months), 30°C/65% RH (12 months; 6 batches) and 40°C/75% RH (6 months; 3 batches). Based on the presented stability data the proposed retest period of 18 months is considered justified. In view of the very hygroscopic and humidity sensitive nature of the drug substance, the precautionary 'Store at 15-30°C protected from light and moisture' is considered justified as well.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, optimization of the formulation and optimization of the manufacturing process. The absence of a bioequivalence study versus the reference product is justified in accordance with the Guideline on the investigation of bioequivalence based on the fact that the product is an aqueous solution at the time of administration, contains qualitatively and quantitatively the same active substance and the differences in excipients compared to the reference product are minimal and not expected to affect gastrointestinal transit, in vivo solubility or in vivo stability. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are sieving of the components, mixing (in two steps) and filling into sachets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scaled batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients comply with their respective Ph.Eur. monographs (saccharin sodium and sucrose) and in-house requirements (orange flavour). All three excipients are controlled for microbiological 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 appearance, water content, appearance of the solution, reconstitution time, pH of the solution, uniformity of dosage units, identity, assay, related substances and microbiological quality. 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 three pilot scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three pilot scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in paper/PE/Al/PE sachets in a carton box. At both storage conditions a consistent increase of impurities is seen, without any clear trends in any of the other tested parameters. The claimed shelf-life of 3 years without any special storage conditions is justified. No in-use

shelf-life after reconstitution is claimed. The reconstituted solution should be used immediately after preparation.

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 Fosfomycine Midas 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 Fosfomycine Midas 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 Monuril 3000, granules for oral solution 3g 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

Fosfomycin 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 submitted no data to support the biowaiver for the 3000 mg powder for oral solution for an *in vivo* bioequivalence study. Instead the MAH stated:
FT-15 sachets has to be administered orally after dissolution of the powder in water. This pharmaceutical form is intended to be administered orally after preparation of an extemporaneous solution in water.
According to the guideline CPMP/EWP/QWP/1401/98 no bioequivalence study is required when the product is administered as aqueous oral solution, containing the active substances at the same concentration as the reference product currently approved.

Before administration the contents of a sachet is dissolved in a glass of water, so the product can be considered as an aqueous oral solution at the time of administration. The test and reference product both contain the same active substance in the same quantity per sachet (i.e. 5.631 g fosfomycin trometamol). The reference product further contains 2,213 g sucrose, mandarin flavour, orange flavour and saccharin (see SmPC Monuril) whereas the test product contains 2,193 g sucrose, saccharin and (only) orange flavour. So, the composition of the test product is comparable to that of the reference product. The differences are considered minimal and not expected to affect gastrointestinal transit, *in vivo* solubility or *in vivo* stability of the active substance and the waiver for bioequivalence testing is considered justified in accordance with the *Guideline on the investigation of bioequivalence* Appendix II.

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 Fosfomycine Midas.

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

Important identified risks	- Hypersensitivity reactions including anaphylactic shock - Pseudomembranous colitis
Important potential risks	None
Missing information	- Use in pregnancy and lactation

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 Monuril 3000, granules for oral solution 3g. 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

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 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

Fosfomycine Midas 3000 mg, powder for oral solution has a proven chemical-pharmaceutical quality and is a generic form of Monuril 3000, granules for oral solution 3g. Monuril is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are administered as an aqueous oral solution use containing the active substances at the same concentration, no bioequivalence study is 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 Fosfomycine Midas with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 December 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