LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Fosfomycin Pharmexon
(fosfomycin trometamol)

SE/H/1673/01/DC

This module reflects the scientific discussion for the approval of Fosfomycin Pharmexon. The procedure was finalised on 2018-04-25. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Pharmexon Consulting SRO has applied for a marketing authorisation for Fosfomycin Pharmexon, 3 g, granules for oral solution. The active substance fosfomycin trometamol is an antibacterial for systemic use. Fosfomycin acts on at the first stage of bacterial wall synthesis.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

No new animal or in vitro studies have been performed with Fosfomycin Pharmexon. This is acceptable since Pharmacodynamic, pharmacokinetic and toxicological properties of fosfomycin trometamol are well known and the use of fosfomycin trometamol is well established in the clinic. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is considered to be adequate even though available non-clinical data seem to be scarce and several deficiencies have been identified. The deficiencies in non-clinical data are considered to be superseded by the long clinical experience with the use of fosfomycin trometamol.

Environmental Risk Assessment (ERA)
The applicant has not showed that no increase in exposure of fosfomycin to the environment is to be expected by introducing Fosfomycin Pharmexon on the market. Instead an Environmental Risk Assessment has been initiated. There are some deficiencies in the performed ERA and additional studies are needed in order to derive a sufficient basis for assessment of a possible environmental effect of fosfomycin. The applicant has submitted a post approval commitment to perform a Dapnia reproduction test, in accordance with OECD guideline 2011, and a test in blue-green algae (Cyanophyta), as recommended in the ERA-Guideline for effects testing of antimicrobials, as well as an Activated Sludge Respiration Inhibition Test in accordance with the OECD Guideline 209. Complete study reports and an updated ERA will be submitted within 1 year after approval. The submitted post approval commitment is considered to be acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical documentation for Fosfomycin Pharmexon includes only bibliographical data. There are no original clinical studies with this specific product.

IV.2 Pharmacokinetics

Most of the pharmacokinetic data included in the application are from studies performed during the 1980s or early 1990s.

Based on comparison of urinary excretion after intravenous and oral administration, oral bioavailability of fosfomycin administered as the fosfomycin trometamol salt varied between 22% and 59% in the cited studies, over a dose range of 2 to 5 gram. Some studies indicated potential dose-dependent absorption, with lower bioavailability at higher doses. Oral bioavailability of fosfomycin trometamol at the 3 gram dose proposed for this product was around 40%. Administration of fosfomycin trometamol with food led to a ca 35% decrease in Cmax, a 30% decrease in AUC, and about 19% increase in Tmax.

Fosfomycin is not protein bound.

Fosfomycin is eliminated almost exclusively via renal excretion, with very little or no metabolism or biliary excretion. It cannot be definitely concluded whether fosfomycin is substrate for renal transport proteins. However, pharmacokinetics of fosfomycin is not

affected by co-administered cimetidine, which suggests that fosfomycin is not a substrate for the renal transporters MATE1/MATE-2K or OCT2.

Data from intravenous administration shows that fosfomycin is rapidly distributed and eliminated. Half-life was generally longer after oral (4-5 hr) than after intravenous (2 hr) administration, indicating absorption-limited elimination at oral administration (flip-flop pharmacokinetic kinetics).

Fosfomycin AUC increased and urinary excretion decreased with decreased renal function. The plasma AUC increased about 4-fold in mild-moderate renal impairment (mean CLcr of 55 ml/min), to 12-fold in severe renal impairment (mean CLcr of 16 ml/min). Half-life increased from 5 hr in healthy subjects to 25 hr in severe renal impairment. The increase in AUC after a single dose is primarily due to prolonged elimination and not to increased plasma levels. The main determinator for efficacy may be urinary concentrations. Therefore, in another study, urinary concentrations were determined in elderly subjects with severe renal impairment (CLcr as low as 20 ml/min). At the normal 3 gram dose, urinary concentrations of fosfomycin, although decreased, were suggested to be above the expected therapeutic levels. No dose adjustment is proposed for subjects with CLcr > 10 ml/min, while the proposed SmPC has a contraindication for use of fosfomycin in patients with CLcr < 10 ml/min, based on expected lack of efficacy in this group. The proposed recommendations for renal impairment are in line with the previously accepted recommendations for Monuril® and are considered well established.

There is no *in vitro* interaction data. Fosfomycin is not expected to be relevantly affected by inhibitors or inducers of metabolism or transport. In an *in vivo* interaction study, metoclopramide by increasing gastric motility affected the extent and rate of absorption of oral fosfomycin, with about 25% and 45% decreases in AUC and Cmax, respectively. The potential of fosfomycin to act as a perpetrator in metabolic or transporter interactions is not known, but lack of data is acceptable given the well-established use of the drug.

The pharmacokinetic data presented by the Applicant is considered sufficient to support making relevant recommendations in the SmPC.

IV.3 Pharmacodynamics

The pharmacodynamic effects of fosfomycin are considered well known. The provided bibliographic data adequately covers the pharmacodynamic aspects. The interaction potential is discussed in more depth in the pharmacokinetic assessment report.

IV.4 Clinical efficacy

The application for Fosfomycin Pharmexon is based solely on bibliographical data. Adequate information regarding the search strategy together with the literature references has been provided; in general the bibliographic data provided cover the efficacy aspects of the product.

The active substance fosfomycin trometamol has been widely used all over the world for several decades. Monuril 2g or 3g granules for oral solution, MAH Zambon S.p.A. is nationally approved in 21 countries within the EU. It has been demonstrated that fosfomycin trometamol in the proposed indications has been in well-established medicinal use within EU for over 20 years with recognised efficacy.

In Sweden, fosfomycin trometamol as Monurol (3 g granules for oral solution) was approved from November 1998 to April 30 2009.

The applicant has applied for a dual indication; treatment of acute lower uncomplicated urinary tract infections in women and adolescent girls above 12 years of age, and prophylaxis in surgical and diagnostic procedures in adult males and females. The submitted literature data covers both indications sought. Overall, the applicant has provided sufficient documentation to support the claimed indications.

IV.5 Clinical safety

This application is based solely on bibliographical data. It has been demonstrated that fosfomycin trometamol has been in well-established medicinal use within EU for over 20 years with an acceptable level of safety. The applicant has provided bibliographic data covering the safety aspects of the product.

Common adverse events associated with fosfomycin trometamol treatments are diarrhoea, headache, nausea and epigastric/abdominal pain. The applicant has provided sufficient discussion regarding the use of fosfomycin trometamol in pregnant women. Overall, the applicant has provided sufficient documentation to support all safety aspects of the product.

IV.6 Risk Management Plans

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 Fosfomycin Pharmexon.

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity reactions Antibiotic-associated diarrhea
Important potential risks	INR alterations
Missing information	-

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

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 language used for the purpose of user testing the PIL was English.
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

The benefit/risk ratio is considered positive and Fosfomycin Pharmexon 3 g, granules for oral solution, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Decentralised procedure for Fosfomycin Pharmexon, 3 g, granules for oral solution was positively finalised on 2018-04-25.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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