Public Assessment Report

Decentralised Procedure

Fosfomycin 3 g granules for oral solution

Procedure No: UK/H/5816/001/DC

UK Licence No: PL 12762/0508

Mercury Pharmaceuticals Limited
Lay Summary
Fosfomycin 3 g granules for oral solution
(fosfomycin, as fosfomycin trometamol)

This is a summary of the public assessment report (PAR) for Fosfomycin 3 g granules for oral solution (PL 12762/0508; UK/H/5816/001/DC). It explains how Fosfomycin 3 g granules for oral solution were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Fosfomycin 3 g granules for oral solution.

For practical information about using Fosfomycin 3 g granules for oral solution, patients should read the package leaflet or contact their doctor or pharmacist.

What are Fosfomycin 3 g granules for oral solution and what are they used for?
Fosfomycin 3 g granules for oral solution are a ‘generic medicine’. This means that Fosfomycin 3 g granules for oral solution are similar to a ‘reference medicine’ already authorised in the European Union (EU) called MONURIL ADULTES 3 g granulés pour solution buvable en sachet.

Fosfomycin 3 g granules for oral solution are used to treat or prevent infections of the bladder. Fosfomycin 3 g granules for oral solution are not suitable for the treatment of children younger than 12 years of age.

How do Fosfomycin 3 g granules for oral solution work?
Fosfomycin 3 g granules for oral solution contain the active substance fosfomycin, as fosfomycin trometamol, which belongs to a group of medicines known as antibiotics. Fosfomycin works by killing bacteria, which can cause infections.

How are Fosfomycin 3 g granules for oral solution used?
Fosfomycin 3 g granules for oral solution should be dissolved in a half glass of water and taken orally, on an empty stomach, preferably before bedtime, after emptying the bladder.

The recommended dose is one sachet (3 g) of Fosfomycin 3 g granules for oral solution as a single dose.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicine can only be obtained with a prescription.

How have Fosfomycin 3 g granules for oral solution been studied?
No additional studies were needed as Fosfomycin 3 g granules for oral solution are a generic medicine that is given as an oral solution and contains the active substance in the same quantity as the reference medicine, MONURIL ADULTES 3 g granulés pour solution buvable en sachet. For this reason Fosfomycin 3 g granules for oral solution is expected to be processed by the body in a similar way to that of the reference medicine.

What are the possible side effects of Fosfomycin 3 g granules for oral solution?
Because Fosfomycin 3 g granules for oral solution are a generic medicine, their benefits and possible side effects are taken as being the same as the reference medicine, MONURIL ADULTES 3 g granulés pour solution buvable en sachet.
For information about side effects that may occur with using Fosfomycin 3 g granules for oral solution, please refer to the package leaflet or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency website.

**Why are Fosfomycin 3 g granules for oral solution approved?**

It was concluded that, in accordance with EU requirements, Fosfomycin 3 g granules for oral solution have been shown to have comparable quality and to be bioequivalent to MONURIL ADULTES 3 g granulés pour solution buvable en sachet. The MHRA, therefore, decided that, as for MONURIL ADULTES 3 g granulés pour solution buvable en sachet, the benefits outweigh the identified risks and recommended that this product can be approved for use.

**What measures are being taken to ensure the safe and effective use of Fosfomycin 3 g granules for oral solution?**

A Risk Management Plan (RMP) has been developed to ensure that Fosfomycin 3 g granules for oral solution are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side-effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Fosfomycin 3 g granules for oral solution**

Luxembourg and the UK agreed to grant a Marketing Authorisation for Fosfomycin 3 g granules for oral solution on 25 June 2015. The Marketing Authorisation in the UK was granted to Mercury Pharmaceuticals Limited on 30 July 2015.

The full PAR for Fosfomycin 3 g granules for oral solution follows this summary.

For more information about the use of Fosfomycin 3 g granules for oral solution, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in September 2015.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States have granted a Marketing Authorisation (MA) for the medicinal product Fosfomycin 3 g granules for oral solution.

This product is a prescription-only medicine (legal status POM) indicated for:

- the treatment of acute uncomplicated lower urinary tract infections in adults, caused by pathogens sensitive to fosfomycin.
- periprocedural prophylaxis in diagnostic and surgical transurethral procedures.

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

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Luxembourg as a Concerned Member State (CMS).

This application was made under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product. The reference medicinal product which has been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area is MONURIL ADULTES 3 g granulés pour solution buvable en sachet; this reference product was authorised to Zambon France, in France on 25 July 1989.

Fosfomycin 3 g granules for oral solution contain the active ingredient fosfomycin, as fosfomycin trometamol. Fosfomycin is a naturally occurring antibiotic, which is synthesised from Streptomyces species. Discovered in 1969, fosfomycin is a small water-soluble molecule with a molecular weight of 138.1 and a simple structure (L-cis-1,2-epoxypropylphosphonic acid), that contains an epoxy group responsible for its antibacterial efficacy. Replacing the two hydrogen atoms in the phosphoric radical with sodium atoms or a calcium atom produces the disodium salt, for parenteral administration, or the calcium salt, for oral use. Fosfomycin trometamol has improved bioavailability compared to the calcium salt.

After active uptake into the bacterial cell, fosfomycin exerts its antibacterial effect by inhibition of cell wall synthesis. Through covalent binding it inhibits the enzyme UPD-N-acetylglucosamine enolpyruvyl transferase, which catalyses the formation of the cell wall building block acetyl-uraminic acid, an early step in wall synthesis. Uptake into the bacterial cell occurs either via the L-α-glycerolphosphate transport system or, if glucose-6-phosphate is present, the hexose phosphate transport system. Fosfomycin is active against a range of Gram-positive and Gram-negative bacteria including some β-lactamase producing strains and those bacteria frequently isolated from urinary tract infection, such as Escherichia coli, Proteus spp., Klebsiella spp., Staphylococcus spp., and Enterococci.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Since Fosfomycin 3 g granules for oral solution are intended for generic substitution, this will not lead to an increased exposure to the environment. An Environmental Risk Assessment
(ERA) is, therefore, not deemed necessary.

According to the EMA *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Cort**) a bioequivalence study may be waived for oral aqueous solutions that contain an active substance in the same concentration as an approved oral solution. The applicant has not submitted a bioequivalence study on this basis and this is acceptable.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 198) on 25 June 2015. After a subsequent National phase, a licence was granted in the UK on 30 July 2015.
II  Quality aspects

II.1  Introduction
This application is submitted according to Article 10(1) of Directive 2001/83/EC, as amended, with MONURIL ADULTES 3 g granulés pour solution buvable en sachet, MAH ZAMBON FRANCE, as a reference product in the Community.

Fosfomycin 3 g granules for oral solution are formulated as white, off-white granules. The granules are presented in paper/low-density polyethylene (LDPE)/aluminium/LDPE sachets, which are further packed into cardboard cartons in quantities of 1 or 2 sachets.

Each single-dose sachet contains 5631 mg fosfomycin trometamol, equivalent to 3 g fosfomycin. The excipients present in the formulation are orange flavour, saccharin sodium, sucrose and calcium hydroxide. The orange flavour consists of: maltodextrin, dextrose monohydrate, acacia (E414), anhydrous citric acid (E330) and butylhydroxyanisole (E320).

II.2  Drug Substance
Fosfomycin trometamol

INN:   Fosfomycin trometamol
Chemical Name:  2-Amino-2-(hydroxymethyl)propane-1,3-diol hydrogen (2R, 3S)-(3-methyloxiran-2-yl) phosphonate

Structure:

\[ \text{Structure} \]

Molecular formula:  \( \text{C}_7\text{H}_{18}\text{NO}_7\text{P} \)
Molecular weight:  259.2
Appearance:   white or almost white, very hygroscopic powder

Fosfomycin trometamol is the subject of a European Pharmacopoeia (Ph Eur) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis. No materials of animal or human origin are used in the production of the active substance.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.
Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical development
The development program was designed to develop a product that is equivalent to the reference product MONURIL ADULTES 3 g granulés pour solution buvable en sachet.

The applicant has justified the absence of a bioequivalence study based on the European Medicines Agency (EMA) Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). This is discussed in section IV.2.

Comparative physico-chemical characteristics have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown.

All of the excipients used in the manufacture of Fosfomycin 3 g granules for oral solution, with the exception of the orange flavour, meet the requirements of the current European Pharmacopoeia. The orange flavour is controlled by a satisfactory in-house specification.

Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients are sourced from animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of this finished product, together with an appropriate account of the manufacturing process. Satisfactory process validation was performed for the manufacturing process. The applicant has committed to perform validation of the first three production scale batches at a new manufacturing site.

Product Specifications
The finished product specification is satisfactory. Satisfactory batch analysis was performed on 10 batches of commercial scale batches of the finished product. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf life, for the unopened sachet, of 3 years. The reconstituted solution should be used immediately. There are no special storage conditions for this product.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended for this application.
III  Non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of fosfomycin are well-known. As fosfomycin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The applicant’s non-clinical overview has been written by an appropriately qualified person. The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate.

Since the formulation of Fosfomycin 3 g granules for oral solution is intended for generic substitution, they will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

There are no major objections to the approval of this application from a non-clinical point of view.

IV  Clinical aspects

IV.1  Introduction
No new clinical data have been submitted and none are required for an application of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2  Pharmacokinetics
No bioequivalence study to compare the test and the reference product has been provided. The applicant has justified the absence of a bioequivalence study based on the EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), which states that ‘if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an oral solution, bioequivalence studies may be waived’. Since Fosfomycin 3 g granules for oral solution are completely soluble in water and the formulation contains the active substance at the same concentration and has the same excipients as the reference product, no bioequivalence study was performed. This is acceptable.

IV.3  Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

IV.4  Clinical efficacy
No new clinical efficacy data are required for this application and none have been submitted.

IV.5  Clinical safety
No new clinical safety data are required for this application and none have been submitted.

IV.6  Risk Management Plan (RMP)
The Marketing Authorisation holder has submitted an RMP, 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 3 g granules for oral solution.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

**Summary table of safety concerns**

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Use in patients with severe renal insufficiency including those undergoing haemodialysis</td>
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<tr>
<td></td>
<td>Use in patients with inability to digest sugars including fructose, sucrose, glucose and galactose</td>
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<tr>
<td></td>
<td>Antibiotic associated colitis</td>
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<tr>
<td></td>
<td>Delayed absorption when taken with food</td>
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<tr>
<td></td>
<td>Interaction with metoclopramide causing lowered serum and urine concentrations</td>
</tr>
</tbody>
</table>

| Important potential risks | Potential effect on patients’ ability to drive or use machinery |

| Missing information | Use in children under 12 years of age |
|                     | Use during pregnancy and lactation |
|                     | Effects on fertility |
### Planned risk minimisation activities

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important Identified Risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypersensitivity</strong></td>
<td>The risks of hypersensitivity associated with the use of the drug product are described in the SPC Sections 4.3, 4.8, and PIL Sections 2, 4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Use in patients with severe renal insufficiency including those undergoing haemodialysis</strong></td>
<td>The risks associated with use of drug product in patients with severe renal insufficiency including those undergoing haemodialysis are described in the SPC Sections 4.3, 4.4, 5.2, and PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Use in patients with inability to digest sugars including fructose, sucrose, glucose and galactose</strong></td>
<td>The risks associated with the use of the drug product in patients with inability to digest sugars including fructose, sucrose, glucose and galactose are described in the SPC Section 4.4 and PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Antibiotic associated colitis</strong></td>
<td>The risks of antibiotic associated colitis with the use of the drug product are described in the SPC Section 4.4 and PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Delayed absorption when taken with food</strong></td>
<td>The risks of delayed absorption of the drug product when taken with food are described in the SPC Sections 4.2, 5.2, and PIL Sections 2 and 3 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Interaction with metoclopramide causing lowered serum and urine</strong></td>
<td>The risks of interaction of the drug product with metoclopramide causing lowered</td>
<td>None</td>
</tr>
</tbody>
</table>
### V.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>concentrations</td>
<td>serum and urine concentrations are described in the SPC Section 4.5 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Important Potential Risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential effect on patients’ ability to drive or use machinery</td>
<td>The risks of potential effect on patients’ ability to drive or use machinery associated with the use of the drug product are described in the SPC Sections 4.7, 4.8, and PIL Sections 2, 4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Missing information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in children under 12 years of age</td>
<td>The SPC Sections 4.2 and PIL Section 2 states that fosfomycin trometamol in a dose of 3 g is not suitable for children under the age of 12 years.</td>
<td>None</td>
</tr>
<tr>
<td>Use during pregnancy and lactation</td>
<td>The SPC Section 4.6 and PIL Section 2 states that there is limited data from the use of fosfomycin in pregnant women. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from fosfomycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.</td>
<td>None</td>
</tr>
<tr>
<td>Effects on fertility</td>
<td>The SPC Section 4.6 states that no clinical data are available for effects of medicinal product on fertility, hence the potential risk for humans is unknown.</td>
<td>None</td>
</tr>
</tbody>
</table>
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 quality of Fosfomycin 3 g granules for oral solution is acceptable and no new non-clinical or clinical safety concerns have been identified.

Oral fosfomycin as an active ingredient has a well-established and acceptable level of safety in the indications approved for the reference product.

The overall benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), package leaflet and labelling are satisfactory, in line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for this product are available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labels are listed below:
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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