Fomicyt 40 mg/ml powder for solution for infusion

(Fosfomycin sodium)

PL 15011/0014

UKPAR

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LAY SUMMARY

Fomicyt 40 mg/ml powder for solution for infusion
(Fosfomycin sodium, powder for solution for infusion, 40 mg/ml)

This is a summary of the Public Assessment Report (PAR) for Fomicyt 40 mg/ml powder for solution for infusion (PL 15011/0014, previously PL 33200/0003). It explains how Fomicyt 40 mg/ml powder for solution for infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Fomicyt 40 mg/ml powder for solution for infusion.

For practical information about using Fomicyt 40 mg/ml powder for solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as Fomicyt in this report.

What is Fomicyt and what is it used for?
Fomicyt belongs to a group of medicines called antibiotics. This medicine contains the active substance fosfomycin (as fosfomycin sodium). Fomicyt is used in adults and children to treat the following infections caused by bacteria, when other antibiotics cannot be used or have not worked:
• infections of the lung;
• infections of the bones;
• infections of the kidney and bladder;
• infections of the brain (meningitis).

Fomicyt is a ‘generic’ medicine. This means that Fomicyt is similar to reference medicines already authorised in the European Union (EU) called Infectofos 2 g and 8 g powder for solution for infusion (InfectoPharm Arzneimittel und Consilium GmbH, Germany).

How does Fomicyt work?
Fomicyt works by killing certain types of germs (bacteria) that cause serious infectious diseases. If left untreated, an infectious disease can spread through the body and may be fatal.

How is Fomicyt used?
Fomicyt can be obtained only with a prescription. The medicine should be taken exactly as advised by the doctor.

Fomicyt is a powder for solution for infusion. Fomicyt, after reconstitution, is given as an infusion into a vein (a drip) by a doctor or a nurse. The infusion will normally take 15 to 60 minutes, depending on the dose.

Usually Fomicyt is given 2, 3 or 4 times a day.
Dosage
The dose that is given and the frequency of the dose will depend on the:
- type and severity of infection that is being treated
- kidney function

In children, it also depends on the child’s:
- weight
- age

The general dosage guidelines for patients with normal kidney function are as follows:

<table>
<thead>
<tr>
<th>Age/weight</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature neonates</td>
<td>100 mg/kg body weight in 2 divided doses</td>
</tr>
<tr>
<td>Neonates</td>
<td>200 mg/kg body weight in 3 divided doses</td>
</tr>
<tr>
<td>Infants 1-12 months (up to 10 kg body weight)</td>
<td>200-300 mg/kg body weight in 3 divided doses</td>
</tr>
<tr>
<td>Infants and children aged 1-12 years (10-40 kg body weight)</td>
<td>200-400 mg/kg body weight in 3-4 divided doses</td>
</tr>
<tr>
<td>Adolescents aged 12-18 years and adults (&gt; 40 kg body weight)</td>
<td>12-24 g in 2-4 divided doses</td>
</tr>
</tbody>
</table>

Individual doses must not exceed 8 g.

The doctor may need to prescribe a lower dose in patients with kidney problems or in patients who are receiving, or require, dialysis.

Duration of treatment
The doctor will decide how long treatment should last, depending on how fast the condition being treated improves.

When treating bacterial infections it is important that the full course of treatment is completed. Even after the fever has passed and the symptoms have abated, treatment should be continued for a few more days.

For further information on how Fomicyt is used, refer to the package leaflet and Summary of Product Characteristics available on the MHRA website.

What benefits of Fomicyt have been shown in studies?
As Fomicyt is a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Infectofos 2 g and 8 g powder for solution for infusion (InfectoPharm Arzneimittel und Consilium GmbH, Germany). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company (Infectopharm Arzneimittel und Consilium GmbH, Germany) has provided data from the published literature on fosfomycin.

What are the possible side effects of Fomicyt?
Because Fomicyt is a generic medicine and is bioequivalent to the reference medicine, the benefits and possible side effects are taken as being the same as those of the reference medicines.
For the full list of restrictions, see the package leaflet available on the MHRA website.

Why is Fomicyt approved?
It was concluded that, in accordance with EU requirements, Fomicyt has been shown to have comparable quality and to be bioequivalent to Infectofos 2 g and 8 g powder for solution for infusion (InfectoPharm Arzneimittel und Consilium GmbH, Germany). Therefore, the MHRA was of the view that, as for Infectofos 2 g and 8 g powder for solution for infusion (InfectoPharm Arzneimittel und Consilium GmbH, Germany), the benefits of Fomicyt are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Fomicyt?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Fomicyt, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Fomicyt.
A Marketing Authorisation (Fosfomycin 40 mg/ml powder for solution for infusion; PL 33200/0003) was first granted in the UK to DLRC Limited on 19 June 2013.

Subsequent to a Change of Ownership procedure, the Marketing Authorisation (Fomicyt 40 mg/ml powder for solution for infusion, PL 15011/0014) was granted in the UK to InfectoPharm Arzneimittel und Consilium GmbH on 16 January 2014.

The full PAR for Fomicyt follows this summary.

For more information about treatment with Fomicyt, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2014.
Fomicyt 40 mg/ml powder for solution for infusion

PL 15011/0014

SCIENTIFIC DISCUSSION

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Clinical assessment ................................ Page 12
Overall conclusions and benefit/risk assessment Page 13
INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Fosfomycin 40 mg/ml powder for solution for infusion (PL 33200/0003) on 19th June 2013. This is a prescription-only medicine (POM) used in treatment of the following infections in adults and children including neonates:

- Acute osteomyelitis
- Complicated urinary tract infections
- Nosocomial lower respiratory tract infections
- Bacterial meningitis
- Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Fosfomycin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of the infections listed above, or when these alternative antibacterial agents have failed to demonstrate efficacy.

This is a national abridged application for Fosfomycin 40 mg/ml powder for solution for infusion submitted under article 10(1) of Directive 2001/83/EC, as amended. This product is cross-referring to Infectofos 2 g and 8 g powder for solution for infusion, authorised to InfectoPharm Arzneimittel und Consilium GmbH, Germany on 8th May 1980 and 28th December 2006, respectively. This reference product is considered valid and in line with EU regulations.

Fosfomycin is a naturally occurring antibiotic which is synthesised from *Streptomyces* species.

Fosfomycin exerts its antibacterial effect by inhibition of cell wall synthesis. Chromosomally mediated resistance leading to reduced uptake into the bacterial cell has been described in both Gram positive and Gram negative organisms. Plasmid mediated resistance (enzymatic inactivation of Fosfomycin) has also been described.

Fosfomycin is reported to possess a low potential for cross resistance with other classes of antimicrobials. *In vitro* data point towards an increased risk of resistance development and Fosfomycin administered intravenously is generally used in combination with other antibacterial agents.

The active ingredient, Fosfomycin, is licensed in the UK as granules for oral administration as a single dose administration in the treatment of lower uncomplicated urinary tract infections. The license is active but the product is not marketed. The intravenous solution does not have a Marketing Authorisation in the UK. Fosfomycin for intravenous administration is however available in several European countries including Germany, Austria, France and Spain.

The applicant has not conducted any clinical studies with the medicinal product. In support of this application, the applicant submitted a large body of data from the literature including more than 60 clinical studies (carried out in more than 1600 patients) as well as in pharmacokinetic and pharmacodynamic data compiled by the company’s clinical expert. During the first round of assessment, several points were raised, particularly concerning the indications and posology of Fosfomycin.

The application was discussed at the Commission on Human Medicines (CHM) meeting in June 2011. The Committee provisionally concluded that further information on efficacy and safety should be requested before the product could be approved. The applicant provided responses to the points raised. Based on the assessment of these responses, the applicant was requested to provide written representation in support of the posology in adults and children as well as in patients with renal failure.
Additional data were generated using a physiology-based pharmacokinetics model (PBPK) and revised dose proposals were submitted in September 2012. The data generally supported the previously submitted data derived from NAD (naïve averaged data) modelling and the dose proposals fell within the range of the posology recommended in other EU member states, where Fosfomycin has been licensed for decades.

This application was also referred to the Chemistry, Pharmacy and Standards Expert Advisory Group (CPSEAG) on 14th June 2011 and 11th September 2012, respectively. All outstanding quality issues have been satisfactorily resolved.

A detailed description of pharmacovigilance system has been provided with this application and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.

Subsequent to a Change of Ownership procedure, the Marketing Authorisation (Fomicyt 40 mg/ml powder for solution for infusion (PL 15011/0014) was granted to InfectoPharm Arzneimittel und Consilium GmbH on 16 January 2014.
UK PAR Fomicyt 40 mg/ml powder for solution for infusion

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature
rINN: Fosfomycin sodium
Chemical Names: Disodium (2R, 3S)-(3-methyloxiran-2-yl) phosphonate
Structure:

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{PO}_3\text{Na}_2 \\
\text{H} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

Molecular Formula: C$_3$H$_5$Na$_2$O$_4$P
Molecular Weight: 182.02 g/mol
Appearance: A white or almost white, very hygroscopic powder.
Solubility: Fosfomycin sodium is very soluble in water, sparingly soluble in methanol and practically insoluble in ethanol and methylene chloride.

The drug substance is the subject of an active substance master file (ASMF). A letter of access has been provided by the drug substance manufacturer.

Synthesis of the drug 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.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other ingredients
The only excipient present in the drug product is succinic acid.

Succinic acid complies with the United States Pharmacopoeia. Satisfactory Certificate of Analysis has been provided for this excipient.

The applicant has confirmed that none of the excipients are of animal or human origin.
**Pharmaceutical development**
Suitable pharmaceutical development data have been provided for this application.

The qualitative and quantitative composition of Fosfomycin 40 mg/ml powder for solution for infusion is identical to the reference product.

**Manufacture**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been satisfactorily validated. Process validation data on commercial batches have been provided. The results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. The Test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The product is supplied in clear type-II glass vials with a rubber stopper and pull-off cap containing 2 g (in 100 ml vial) or 8 g (in 250 ml vial) of Fosfomycin, respectively, in packs of 10 vials each.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 4 years with a storage condition “Keep the vial in the outer carton in order to protect it from light” have been set. These are satisfactory.

After reconstitution: From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, unless reconstitution has taken place in controlled and validated aseptic conditions.

A reconstituted solution that has been produced under aseptic conditions is chemically stable in a refrigerator (at 2-8°C) for at least 12 hours, if protected from light.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

**Marketing Authorisation Application (MAA) Form**
The MAA form is pharmaceutically satisfactory.
Expert Report/Quality Overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of fosfomycin sodium are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

An environmental risk assessment (ERA) has been performed. This is satisfactory.

There are no objections to the approval of this product from a non-clinical point of view.
CLINICAL ASSESSMENT

III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), a bioequivalence study is not required if the test product is an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence study has been submitted with this application and none is required.

No new data have been submitted and none are required for applications of this type.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.

Clinical safety
Fosfomycin sodium has an acceptable adverse event profile. No new safety data were supplied or required for this generic application. Fosfomycin sodium has a well-established side-effect profile and is generally well-tolerated.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form
The MAA form is medically satisfactory.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

QUALITY
The important quality characteristics of Fosfomycin 40 mg/ml powder for solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new efficacy data were submitted and none are required for applications of this type. As the safety profile of fosfomycin sodium is well-known, no additional data were required. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory.

BENEFIT RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with fosfomycin sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
**Fomycyt 40 mg/ml powder for solution for infusion**

**PL 15011/0014**

### STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation application for Fosfomycin 40 mg/ml powder for solution for infusion on 21st January 2010</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 28th January 2010</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality and clinical dossier on 7th May 2010</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to MHRA’s requests providing further information to the quality and clinical issues on 31st January 2011</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 19th June 2013.</td>
</tr>
</tbody>
</table>
Fomicyt 40 mg/ml powder for solution for infusion

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

The following table lists a non-safety update to the Marketing Authorisation (Fomicyt 40 mg/ml powder for solution for infusion, PL 15011/0014) for this product that has been approved by the MHRA since the product was first licensed. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 August 2014</td>
<td>Type II</td>
<td>To update section 4.2 (Posology and method of administration) of the Summary of Product Characteristics (SmPC), from ‘The first dose should be increased by 100% (loading dose)’ to ‘The first dose should be increased by 100% (loading dose), but must not exceed 8 g’. This is a minor editorial change to make the dosing recommendation more clear.</td>
<td>Approved 01 September 2014.</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
FOMICYT™ 40 mg/ml
Fosfomycin Powder for solution for infusion
2 g in 50 ml after reconstitution
For intravenous use.

One vial with 2.69 g of powder contains 2.64 g fosfomycin,
(corresponding to 2 g fosfomycin) and 0.05 g (20 mmol) sodium,
for the reconstitution in 50 ml of solvents. One vial of
reconstituted solution contains 49 mg fosfomycin.
Effective: See section 5.1.3.

Keep the package intact before use. Use only clear solusions.
Keep the vial in the outer carton in order to protect it from light.
The reconstituted solution should be used immediately or stored in
a refrigerator (at 2-8 °C) protected from light for up to 12 hours.
Any remaining solution should be discarded.
Keep out of the sight and reach of children.
UK PAR Fomicyt 40 mg/ml powder for solution for infusion

For intravenous use.
Keep out of the sight and reach of children.

Distributor: NORDIC PHARMA
Arzneimittel und Consilium GmbH,
Von-Humboldt-Str. 1, 64666 Heppenheim, Germany

One vial with 2.69 g of powder contains:
- 2.64 g disodium fosfomycin, corresponding to 2 g fosfomycin and 0.64 g (28 mmol) sodium, for the reconstitution in 50 ml of solvent.
- One ml of reconstituted solution contains 40 mg fosfomycin.

Excipient: Succinic acid.

Read the package leaflet before use. Use only clear solutions. Keep the vial in the outer carton in order to protect it from light. The reconstituted solution should be used immediately or stored in a refrigerator (at 2–8°C) protected from light for up to 12 hours, if reconstituted under aseptic conditions. Any remaining solution should be discarded.

PL 15011/0014 732100412E02

For intravenous use.
Keep out of the sight and reach of children.

Distributor: NORDIC PHARMA
Arzneimittel und Consilium GmbH,
Von-Humboldt-Str. 1, 64666 Heppenheim, Germany

One vial with 5.38 g of powder contains:
- 5.28 g disodium fosfomycin, corresponding to 4 g fosfomycin and 1.28 g (56 mmol) sodium, for the reconstitution in 100 ml of solvent.
- One ml of reconstituted solution contains 40 mg fosfomycin.

Excipient: Succinic acid.

Read the package leaflet before use. Use only clear solutions. Keep the vial in the outer carton in order to protect it from light. The reconstituted solution should be used immediately or stored in a refrigerator (at 2–8°C) protected from light for up to 12 hours, if reconstituted under aseptic conditions. Any remaining solution should be discarded.

PL 15011/0014 732100422E01
Fomicyt™ 40 mg/ml

Fosfomycin Powder for solution for infusion

8 g in 200 ml after reconstitution

For intravenous use.

Read the package leaflet before use. Use only clear solutions. Keep the vial in the outer carton in order to protect it from light. The reconstituted solution should be used immediately or stored in a refrigerator (at 2-8°C) protected from light for up to 12 hours, if reconstituted under aseptic conditions. Any remaining solution should be discarded.

Keep out of the sight and reach of children.

Distributor: NORDIC PHARMA
Arzneimittel und Consilium GmbH,
Von-Humboldt-Str. 1, 64466 Heppenheim, Germany

POM

NORDIC PHARMA

Mock_up_fomicyt_8g/09-V

EXP Batch

PL 15011/0014
Annex 1

Our Reference: PL 15011/0014, Application 10
Product: Fomicyt 40 mg/ml powder for solution for infusion
Marketing Authorisation Holder: InfectoPharm Arzneimittel und Consilium GmbH
Active Ingredient(s): Fosfomycin sodium.

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable):

Reason:
To update section 4.2 (Posology and method of administration) of the Summary of Product Characteristics (SmPC), from ‘The first dose should be increased by 100% (loading dose)’ to ‘The first dose should be increased by 100% (loading dose), but must not exceed 8 g’. This is a minor editorial change to make the dosing recommendation more clear.

Linked / Related Variation(s) or Case(s):
N/A

Supporting Evidence
Revised SmPC has been provided.

Evaluation
The updated section of the SmPC is satisfactory.

Conclusion
The amendment to the SmPC is acceptable and there are no objections to approval.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision - Approved on 01 September 2014