6.2. Elements for a Public Summary

6.2.1. Overview of disease epidemiology

Fomicyt 40 mg/ml powder for solution for infusion is authorised for intravenous administration as a second line option for the treatment of bacterial infections, including osteomyelitis, complicated urinary tract infections, nosocomial lower respiratory tract infections, bacterial meningitis, and bacteraemia associated with any of the infections mentioned above.

Osteomyelitis

- Osteomyelitis or osteitis is an infection of the bone which can occur at any age, usually caused by bacteria. Bacteria causing osteomyelitis may enter the bone from the bloodstream or through an injury or during orthopaedic surgery.
- It is estimated that in Western Europe around 9-10 of 100,000 inhabitants per year will visit a hospital for osteomyelitis (e.g. 5,000 people each year in England) [1].

Complicated urinary tract infection

- Urinary tract infections comprise infections of the kidneys and the bladder caused by various bacteria.
- They belong to the most common bacterial infection in the general population. In the United States urinary tract infections accounted for nearly 7 million office visits each year and 1 million emergency department visits resulting in 100,000 hospitalisations [3].

Nosocomial lower respiratory tract infections

- Nosocomial or hospital-acquired pneumonia is defined as a lung infection with first clinical symptoms occurring earliest 48 hours of admission to the hospital or appear weeks to months after discharge from hospital [2].
- In the Intensive Care Unit the number of infections of the lung for patients receiving mechanical ventilation was 5.4 per 1,000 ventilator days. For patients not receiving mechanical ventilation the number of lung infections was 0.6 per 1,000 patient days. In addition lung infections come from patients of the Intensive Care Unit who were not ventilated and from patients from other units. All together it is estimated that there are approximately 40,000 hospital-acquired lung infections per year in Germany [2].

Bacterial meningitis

- Meningitis is a disease caused by the inflammation and swelling of the protective membranes covering and protecting the brain and spinal cord known as the meninges. This is usually caused by an infection of the fluid surrounding the brain and spinal cord caused by bacterial germs (pathogens). Bacterial meningitis is a life-threatening condition that requires prompt recognition and treatment with antibiotics [4, 5, 6, 7].).

- The incidence in Western Europe is estimated with 3 to 5 cases per 100,000 inhabitants per year (e.g. 2,000 to 3,200 cases per year in the United Kingdom). Incidence is higher in children (around 21 of 100,000 children per year).

Bacteraemia associated with any of the infections mentioned above

- All of the infections described above, i.e. complicated urinary tract infections, nosocomial lower respiratory tract infections, and even more frequently acute osteomyelitis and bacterial meningitis, may be associated with bacteraemia, which is defined as the presence of bacterial pathogens in the blood.
- Bacteraemia can have severe complications including life threatening systemic immune reaction which is called sepsis, septic shock, or infection of different organs distinct from the original source of the bloodstream infection.

6.2.2. Summary of treatment benefits

Fosfomycin belongs to a group of medicines called antibiotics. It works by killing certain groups of germs (bacteria) that cause serious infectious diseases. If left untreated, an infectious disease can spread through the patient's body and may be fatal. It is important that the patient receives an effective treatment for this condition. Fosfomycin is given as an infusion into a vein (a drip) by a doctor or a nurse.

Fosfomycin has been used for more than 40 years for intravenous treatment of severe and complicated bacterial infections. Efficacy and safety of fosfomycin have been established in more than 60 clinical trials (carried out in more than 1,600 patients) mostly performed in the 1970s and 1980s. An improvement of disease was shown in a considerable number of these studies and a favourable effect was also seen with respect to the eradication of bacteria. Microbiological surveys over the past decades indicate that there has been only rather small changes in the activity of fosfomycin against the relevant pathogens, including problematic organisms, which are resistant to standard antibiotic regimens. Therefore, fosfomycin is indicated when it is considered inappropriate to use standard or first line antibacterial agents, or when these alternative antibacterial agents have failed to demonstrate efficacy.

6.2.3. Unknowns relating to treatment benefits

Fosfomycin is a treatment option when it is considered inappropriate to use standard or first line antibacterial agents, or when these alternative antibacterial agents have failed to demonstrate efficacy. The reason for fosfomycin being regarded as a so-called "second line antibiotic" is the limited clinical data base available to support the efficacy and safety of this antibiotic, as already addressed in section 6.2.2. In particular, dosing recommendations for children and for patients with renal impairment (kidney problems) are based on limited clinical data. Safety and efficacy have not been studied in children with different stages of kidney failure. Dosing recommendations for adult patients on renal replacement therapy (e.g. dialysis) are only available for some but not all of the different procedures established to help people with kidney failure.

Fosfomycin may be used for the treatment of infections with bacteria which are resistant to other antibiotics. However, resistance to fosfomycin has also been reported.

6.2.4. Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
High levels of blood sodium or low levels of blood potassium (hypernatraemia and/or hypokalaemia)	The fosfomycin solution contains high levels of sodium which is brought into the bloodstream by infusion and in turn may cause potassium to be cleared from the blood excessively. These effects occur uncommonly (affecting less than 1 person in 100) and may be recognised by symptoms such as confusion, muscle twitching or abnormal heart rhythm. Patients who have a high sodium blood level before fosfomycin treatment are at special risk.	Yes, doctors are advised to consider recommending a low-sodium diet, supplementing potassium, and monitoring serum sodium and potassium levels and water balance during treatment. Fosfomycin should be used with caution in patients with heart problems, high blood pressure, a certain disorder of the hormone system (hyperaldo-steronism), high levels of blood sodium before treatment and fluid accumulation in the lungs (pulmonary oedema). The patient should tell his/her doctor right away if confusion, muscle twitching or abnormal heart rhythm should occur.
Serious allergic reaction (anaphylactic shock)	Serious allergic reactions may occur very rarely (affecting less than 1 person in 10 000). They may be recognised by symptoms such as breathing or swallowing problems, sudden wheezing, dizziness, swelling of eyelids, face, lips or tongue, rash or itching.	No, patients with known allergy to fosfomycin should not be treated with this antibiotic and patients are advised to tell their doctor straight away if symptoms of an allergic reaction should occur. In this case, the infusion may have to be stopped immediately.
Serious bowel inflammation (pseudomembranous colitis)	Pseudomembranous colitis, presenting as a severe and persistent diarrhoea which may be associated with abdominal pain or fever, may occur, but the frequency cannot be	No, patients are advised to tell their doctor immediately, when severe and persisting diarrhoea with or without fever should occur during or

	estimated from the available data. Pseudomembranous colitis has been reported with nearly all antibacterial agents including fosfomycin, and may range in severity from mild to life-threatening. This kind of bowel inflammation is caused by specific bacteria called *Clostridium difficile.*	shortly after fosfomycin treatment. In this case, fosfomycin treatment may have to be stopped immediately and the doctor will consider specific treatment against the bacteria causing pseudomembranous colitis. Patients are advised to tell their doctor immediately, when severe and persisting diarrhoea with or without fever should occur. In this case, patients should not take medicines against diarrhoea that inhibit the bowel movements (antiperistaltics).
Use in patients with reduced kidney function (renal impairment)	Fosfomycin is excreted via the kidneys.	Yes, the dosage of fosfomycin may have to be modified if the patient's kidney function is moderately to severely reduced. Patients are recommended to inform their doctor about kidney problems.
Adverse reactions affecting the liver (hepatotoxicity, including fatty liver and hepatitis)	High levels of blood liver enzymes, possibly associated with liver problems, may occur uncommonly (affecting less than 1 person in 100). More rarely, liver problems such as fatty liver and liver inflammation (hepatitis) may occur.	No, patients are recommended to tell their doctor straight away if they notice yellowing of the skin or the whites of their eyes (jaundice) which can be an early sign of liver problems.
Adverse reactions affecting the blood and lymphatic system (haematological reactions, including aplastic anaemia, agranulocytosis and pancytopenia)	Haematological reactions, including severe reduction in blood cells which can cause weakness, bruising or make infections more likely (aplastic anaemia) and severe reduction in number of white cells which makes	No, patients are recommended to tell their doctor straight away if they notice pale skin, weakness or breathlessness and/or bleeding, bruising and more infections as usual which is possibly due to a reduction

	infections more likely (agranulocytosis) or severe reduction in blood cells which can cause weakness, bruising or make infections more likely (pancytopenia) may occur rarely (affecting less than 1 person in 1000) and with unknown frequency, respectively. They may be recognised by symptoms such as pale skin, weakness or breathlessness and bleeding, bruising and acquiring more infections as usual, respectively.	in blood cells and/or could be caused by a low number of white blood cells or blood platelets.

Important potential risks

Risk	What is known *(Including reason why it is considered a potential risk)*
Development of resistance	As many other antibacterial agents the effectiveness of fosfomycin can decrease over time because bacteria can develop resistance to this drug. Resistance to fosfomycin in bacteria has been described but may vary geographically and with time for selected species. Patients are advised that their doctor decides on treatment duration and that it is important to complete the full course of treatment as advised by their doctor. Combining fosfomycin with other antibiotics may reduce the occurrence of resistant bacteria during treatment.
Intra-arterial administration	As damaging effects can result from inadvertent intra-arterial administration of fosfomycin, it is essential to ensure that fosfomycin is only administered into veins. Patients are informed that fosfomycin is given as an infusion into a vein by a doctor or a nurse. Doctors are instructed to administer fosfomycin only into veins.

Missing information

Risk	What is known
Use in pregnant or lactating women	There are limited information on the safety of fosfomycin in pregnant women. However, it is known, that fosfomycin is transferred from the maternal to the foetal circulation system. Recommendation is given that fosfomycin should not be prescribed to pregnant women unless the benefit outweighs the risk.

	Fosfomycin levels in human milk are low (about 8 % of the blood concentrations). Fosfomycin should therefore not be administered during lactation, unless the benefit outweighs the risk.
Use of fosfomycin in children with kidney problems (renal impairment)	No dose recommendations can be made for children with renal impairment. Clinical data for children and neonates with renal impairment are currently lacking. Safety and efficacy have not yet been evaluated in clinical trials. Patients are advised to inform their doctor about kidney problems.
Limited safety data in particular with high doses in excess of 16 g/day	There is currently only limited information available on the safety of fosfomycin in particular with high doses in excess of 16 g/day. Individual doses must not exceed 8 g. Patients are advised to ask a medical professional immediately if they think that they have been given too much fosfomycin. Moreover, patients are recommended to contact their doctor immediately if certain dose related adverse effects (e.g. severe and persistent diarrhoea, jaundice, confusion, muscle twitching or abnormal heart rhythm) should occur.

6.2.5. Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, its risk, and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics (SmPCs) and the Package leaflet for Fomicyt 40 mg/ml powder for solution for infusion authorised to Infectopharm by the Medicines and Healthcare Products Regulatory Agency (MHRA) can be found at:

http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm

This medicine has no additional risk minimisation measures.

6.2.6. Planned post-authorisation development plan

Due to the well known safety and efficacy profile of fosfomycin, there are currently no post-authorisation studies planned.

6.2.7. Summary of changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comment
1.0	31 DEC 2014	Identified Risks • High levels of blood sodium or low levels of blood potassium (hypernatraemia and/or hypokalaemia) • Serious allergic reaction (anaphylactic shock) • Serious bowel inflammation (pseudomembranous colitis) • Use in patients with reduced kidney function (renal impairment) • Intra-arterial administration • Adverse reactions affecting the liver (hepatotoxicity including fatty liver and hepatitis) • Adverse reactions affecting the blood and lymphatic system (haematological reactions, including aplastic anaemia, agranulocytosis and pancytopenia) Potential Risks • Development of resistance Missing Information • Pregnant or lactating women • Use in children with renal problems (renal impairment • Limited safety data in particular with high doses in excess of 16 g/day	This RMP constitutes the second RMP for fosfomycin-containing products for which InfectoPharm holds marketing authorisations.
1.0	10 APR 2015	Change of intra-arterial administration from identified risk to potential risk	
1.0	26 May 2015	- Comment on combination therapy was removed from part I product overview in line with the updated SmPC - Dosing section was adapted to updated SmPC (clarification that loading dose in patients with renal impairment must not exceed 8 g). - Since tradenames in the different countries vary, the placeholder <TRADENAME> was included instead of “Fomicyt” or “Fosfomycin”. - Editorial corrections and adaptions of cross-references. - Update of Annex 2 (updated SmPC)	

1.0	01 June 2015	- Inclusion of tradename in RMS on cover page	
1.0	02 June 2015	- Inclusion of all invented names of the product as requested by the MHRA	
1.0	08 June 2015	- Update of Annex 2 (updated SmPC and PIL)	