Part VI: Summary of the risk management plan by product

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Urinary tract infections (UTI) are very common and an important clinical problem. In the US nearly 7 million patients sought medical treatment because of urinary tract infections in 1997, including 2 million cases of bladder infection (Foxman 2002). In Europe, such data is not available, but data obtained from the US can be applied with caution to the European situation.

Women are more likely to get urinary tract infections than men. Nearly one in three women will have had at least one urinary tract infection requiring antibiotic treatment by the age of 24 years. Almost half of all women will experience a urinary tract infection during their lifetime. Infants, pregnant women, the elderly and patients with spinal cord injuries, catheters, diabetes, multiple sclerosis, AIDS, HIV or with abnormalities in the urinary system are more likely to get urinary tract infections. In elderly, urinary tract infections are the second most common form of infection, accounting for nearly 25% of all infections. Urinary tract infections in patients with catheters is the most common hospital-acquired infection, accounting for >1 million cases in hospitals and nursing homes in the US yearly (Foxman 2002).

Upper urinary tract infections (i.e., acute pyelonephritis) may lead to kidney pain, high blood pressure, and end-stage of state of improper kidney function (UTI 2012). Urinary tract infections reflect an infection of the urinary system causing an inflammatory response (Dason 2011). The treatment of urinary tract infections is managed by antibiotic therapy. Single oral dose therapy with fosfomycin trometamol (2 g in children > 6 years and 3 g in adults) is recommended in the treatment of uncomplicated urinary tract infection (Naber 2012).

VI.2.2 Summary of treatment benefits

Fosfomycin trometamol is an orally active bactericidal (drug that kills bacteria) which is active against all strains of Escherichia coli (bacteria living in the gut) (Chidiamara 2014) (Raz 2012) and it is not structurally related to other classes of antimicrobial agents (Pérez 2013). Fosfomycin trometamol appears to be little cross resistance (clinical phenomenon whereby a previously effective antibiotic no longer works because the target pathogen has developed a defense against it) with other antimicrobial agents, possibly due to its chemical structure and action site are different from other agents (Pérez 2013).

This medicinal product has a unique action that involves the interruption of cell-wall synthesis. Fosfomycin has a large antimicrobial activity, including activity against several Gram-negative and Gram-positive aerobic bacteria (Falagas 2010) (Raz 2012). Fosfomycin also decreases bacteria adherence to uroepithelial cells (Fosfomycin review).

Fosfomycin trometamol is used for patients with acute bacterial infections. The use of fosfomycin in humans has been suggested due to its low toxicity and potential efficacy. It is well tolerated, with a low incidence of adverse events and rapid bactericidal effect (Pérez 2013).

VI.2.3 Unknowns relating to treatment benefits

There is no evidence to suggest that fosfomycin trometamol cannot be applied in the target population (patients with acute not complicated infections of low urinary tract). However, there is limited information in pediatric population younger than 6 years and safety in pregnancy and breastfeeding. Therefore, Fosfomycin trometamol should be administered according to indications and warnings included in the proposed product information (SmPC and PL).

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions (hypersensitivity reactions)	An allergy is a hypersensitivity disorder of the immune system. Allergic reactions occur when a person's immune system reacts to some substances. These reactions are acquired, predictable, and rapid. Allergic reactions are distinctive because of excessive activation of certain white blood cells called mast cells and basophils by a type of antibody called Immunoglobulin E. This reaction results in an inflammatory response which can range from uncomfortable to dangerous.	The proposed SmPC and PL contain the proper information to minimize the risk of this risk. A contraindication for the use in patients hypersensitive to fosfomycin trometamol is included in section 4.3 of the SmPC. A warning regarding hypersensitivity reactions is included in section 4.4 of the SmPC. Anaphylactic reactions (including anaphylactic shock) and hypersensitivity are listed in Section 4.8 of the SmPC. The PL sections are aligned with the above information in the SmPC.
Diarrhoea upon administration of antibiotics (pseudomembranous colitis)	Pseudomembranous colitis is an inflammation of the colon that occurs in some people who have taken antibiotics. Treatment with an antibiotic may affect the normal bacterial flora in the colon, and colonisation with the bacteria Clostridum difficile may occur. The bacteria release toxins which may result in diarrhoea and inflammation of the colon (colitis). When adherent yellow or white plaques, pseudomembranes, are present on the intestinal mucosa the disease is called pseudomembranous colitis.	A warning regarding pseudo-membranous colitis is included in section 4.4 of the SmPC. Pseudomembranous colitis is listed in section 4.8 of the SmPC. The PL sections are aligned with the above information in the SmPC.

Important potential risks

Not applicable.

Missing information

Risk	What is known (Including reason why it is considered a potential risk)
Pregnancy	There are no adequate and well-controlled studies with fosfomycin in pregnant women. Fosfomycin crosses the placenta. Studies in animals have not shown reproductive toxicity. Fosfomycin should only be used during pregnancy if clearly indicated.
Breastfeeding	Fosfomycin is excreted in low concentrations in breast milk. Diarrhoea and fungal infections of the mucous membranes as well as sensitisation could occur in the breast-fed infant. Women who are breastfeeding should be treated only if clearly indicated. Fosfomycin trometamol is contraindicated in children younger than 6 years old.

VI.2.5 Summary of risk minimisation activities by safety concern

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

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation

No applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

This report corresponds to the first RMP according Directive 2010/84/EC, amending Directive 2001/83/EC, Commission Implementing Regulation (EU) No. 520/2012 and Good Pharmacovigilance Practices.