NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Germany:

Product Name	Fosfomycin-containing medicinal products
Active substance(s)	Fosfomycin trometamol Fosfomycin calcium Fosfomycin disodium Fosfomycin sodium
Pharmaceutical form(s)	Pharmaceutical forms for systemic use
Strength(s)	All
Route of administration(s)	Oral, intramuscular and intravenous
Marketing Authorisation Holder(s)	Various

Fosfomycin is a naturally occurring antibiotic agent, discovered in 1969. Fosfomycin exerts a bactericidal effect by irreversible inhibition of enolpyruvate transferase (MurA), which prevents the formation of N-acetylmuramic acid, an essential element of the peptidoglycan cell wall. It displays bactericidal activity against a wide spectrum of Gram-positive and Gram-negative bacteria, including ESBL-producing enterobacteria, methicillin-resistant S. aureus (MRSA), glycopeptide-resistant enterococci and multidrug-resistant enterobacteria.

Fosfomycin-containing products are available in different pharmaceutical forms: fosfomycin tromethamine (a soluble salt) and fosfomycin calcium for oral use, as well as fosfomycin disodium and fosfomycin sodium for intravenous use. In addition, single products for intramuscular injection containing fosfomycin are available.

Fosfomycin trometamol (a widely used synonym for tromethamine) is the active substance intended for oral administration and is provided in single-dose sachets that contain 2 g or 3 g fosfomycin. Fosfomycin trometamol is approved in most EU countries.

Fosfomycin calcium represents the active component of the 500 mg tablets of fosfomycin. Fosfomycin calcium is nationally authorized in Spain only and thus not commercially available in other EU member states.

The intravenous fosfomycin formulation consists of 1 to 8 g powder of fosfomycin disodium or fosfomycin sodium with succinic acid as the sole excipient and is available in most EU countries. The intramuscular fosfomycin formulation is nationally authorized in Spain only.

Oral fosfomycin is mainly used for the treatment for uncomplicated urinary tract infections (UTIs) caused by pathogens sensitive to fosfomycin in adult and adolescent females. However, oral fosfomycin is also approved for prophylaxis in diagnostic and surgical transurethral procedures in some EU countries.

Intravenous fosfomycin is approved for the treatment of osteomyelitis, complicated urinary tract infections, nosocomial lower respiratory tract infections, bacterial meningitis, and bacteraemia that occurs in association with these infections in adults and children including neonates. Intravenous fosfomycin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections, or when these alternative antibacterial agents have failed to demonstrate efficacy.

Intramuscular fosfomycin is approved for various indications such as adnexitis, endometritis, genitourinary tract infections or prophylaxis.

The treatment of bacterial infections is hampered worldwide by the global spread of multidrug-resistant (MDR) or extensively drug-resistant (XDR) Gram-positive and Gram-negative pathogens and the lack of development of new antibiotics active against such MDR and XDR bacteria. Therefore, the implementation of alternative treatment strategies such as the reevaluation of older antibiotic agents seems to be an appealing option. In this context, interest in fosfomycin has undergone a revival in recent years as it has a unique mode of action as well as a unique chemical structure that makes cross-resistance uncommon and allows for additive and synergistic activities with other antibiotics. However, there are only limited clinical data comparing clinical efficacy of fosfomycin with current standard therapy regimens.

In addition, as is the case with many antibacterial agents which were approved decades ago, there are significant differences between the product information of fosfomycin-containing products across the European Member States, in particular in the approved indications and posology, but also in other sections of the Product Information. For example, for intravenous fosfomycin variety of approved indications differs significantly and the wording of several

indications in many European Member States is too broad. Another example is that for oral fosfomycin the indication prophylaxis in diagnostic and surgical transurethral procedures was approved in some European countries, whereas in other countries this indication was regarded as not appropriate.

Overall, there is a need to reevaluate the benefit-risk ratio of the approved indications considering the current scientific knowledge. Furthermore, the appropriate dose and duration of administration for oral, intravenous and intramuscular formulations need to be discussed as well as the adequacy of safety relevant information and information about pharmacological properties.

In view of the above and given the necessity to take action at the EU level, Germany considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

Signed

Date 7th December 2018

[redacted]

President of BfArM