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PRODUCT FOCUS

# Focus on fosfomycin trometamol

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## Introduction

Fosfomycin, a phosphonic acid derivative and a naturally-occurring antibiotic, was discovered in 1969 when it was successfully cultured from *Streptomyces* spp.[1,2] Fosfomycin is in an antimicrobial class of its own and is structurally unrelated to any other agent currently approved for clinical use.[3]

Fosfomycin was initially developed as a calcium salt for oral use and a sodium salt for intravenous use.[4] The tromethamine salt (also known as trometamol) is water soluble and provides markedly improved oral bioavailability compared to the calcium salt.[4]

## Indication

Fosfomycin trometamol (Urizone®) is indicated as a single dose in the treatment of acute uncomplicated lower urinary tract infections (UTIs) caused by sensitive *Escherichia coli (E. coli)* in women and female children over the age of five years.[5] Fosfomycin trometamol is also indicated for prophylaxis in diagnostic and surgical transurethral procedures in adult men.[5]

## Mechanism of action

Fosfomycin is a bactericidal antibiotic.[1] It inhibits an enzyme-catalysed reaction in the first step of the synthesis of the bacterial cell wall.[1] Fosfomycin irreversibly blocks bacterial cell wall synthesis at an earlier stage than beta-lactams or glycopeptide antibiotics.[6]

Fosfomycin's mechanism of action is distinct from other bacterial cell wall inhibitors (such as the beta-lactams and glycopeptides) as well as other classes of antibacterial agents, suggesting that the likelihood of cross-resistance to these other agents should be minimal.[2] Indeed, there appears to be little cross-resistance between fosfomycin and other antibacterial agents, possibly because it differs from other agents in its general chemical structure and site of action.[4] Fosfomycin has remained active against both Gram-positive and Gram-negative multidrug-resistant and extensively drug-resistant pathogens.[1]

The antimicrobial spectrum of fosfomycin is broad and it exhibits bactericidal activity against both Gram-positive and Gram-negative bacteria.[5,6] It is particularly active against *E. coli, Enterobacter, Klebsiella, Serratia* and *Enterococcus* spp.[4] *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa* and *Proteus mirabilis,* are among many other bacteria against which fosfomycin is antimicrobially active.[6]

Fosfomycin, therefore, has a broad spectrum of activity encompassing most urinary tract pathogens isolated from patients with lower urinary tract infections.[4]

*E. coli* is the most common bacterial cause of community-acquired (~72% of cases) and hospital-acquired (~51% of cases) UTIs in South Africa.[7] *Klebsiella pneumoniae* causes at least 9% of community-acquired and at least 17% of hospital-acquired UTIs.[7]

## Efficacy of fosfomycin in urinary tract infections

Fosfomycin is mainly used in the treatment of uncomplicated UTIs.[4] In clinical trials in patients with acute uncomplicated lower UTIs, single-dose fosfomycin was effective and comparable with several other antibacterial agents given either as a single-dose or as multiple-dose treatments (e.g. beta-lactams, fluoroquinolones, cotrimoxazole and nitrofurantoin).[4,7] In three large double-blind comparisons with ciprofloxacin, cotrimoxazole and nitrofurantoin, 99% of fosfomycin-treated patients and 100% of patients receiving comparator agents were considered clinically cured or improved after therapy.[4]

Because *E. coli* is the most frequent bacterial cause of community-acquired UTIs, the antimicrobial susceptibility of *E. coli* must be taken into consideration. *E.coli* susceptibility data cultured by Ampath Laboratories in South Africa from outpatient urine in 2021, show a 97% susceptibility of *E. coli* to fosfomycin.[8] However, fosfomycin should not be used if there is any suspicion of early pyelonephritis, since it does not achieve adequate renal tissue levels.[7]

The Infectious Diseases Society of America recommends that the resistance percentages of the causative pathogens should be < 20% to consider an antibiotic as a suitable treatment for a lower UTI.[9]

## Pharmacokinetic properties

In the formulation as the trometamol salt, fosfomycin is well-absorbed orally and has an oral bioavailability of 34–41%.[4] Following a single 3-gram oral dose, peak urinary and bladder tissue concentrations occur within four hours and remain high (> 128 mg/L) for 36 hours or more, which is sufficient to inhibit most urinary tract pathogens.[1,4,5] Food delays and reduces the absorption of fosfomycin trometamol, resulting in reduced blood and urinary concentrations.[5]

Fosfomyin has a mean elimination half-life of 5.7 hours and is primarily excreted unchanged via the kidneys in the urine.[4] This results in high peak urinary concentrations within two to four hours which are maintained for at least 36 hours.[5] In patients with moderately reduced renal function (creatinine clearance > 80 ml/min), including the physiological reduction in the elderly, the elimination half-life is prolonged, but urinary concentration remains therapeutically adequate.[5] Fosfomycin trometamol is contraindicated in patients with severe renal insufficiency (creatinine clearance < 10 ml/min).[5]

## Administration

Fosfomycin trometamol is administered orally after reconstitution in water.[5] It is available as 2-gram and 3-gram sachets.

The recommended dose for uncomplicated UTIs (cystitis) in women, including the elderly up to the age of 75 years, is a single 3-gram dose.[5] Female children over the age of five years should be given a single 2-gram dose.[5] The recommended dose for prophylaxis prior to transurethral surgical and diagnostic proceduress in adult men, including the elderly, is two doses of 3-gram.[5] The first dose should be taken three hours before surgery and the second dose should be taken 24 hours after surgery.[5] Since food delays and reduces the absorption of fosfomycin trometamol, it should be taken at least two hours before the next meal.[5]

Fosfomycin has minimal interactions with other medicines.[3] Concomitant administration of metoclopramide is not advised, since it has been shown to lower serum and urinary concentrations of fosfomycin trometamol.[4,5]

## Use in pregnancy

No evidence in animals or humans has been found to indicate adverse effects of fosfomycin trometamol in pregnancy. However, the safety and efficacy of single-dose therapy has not been established in pregnancy.[5] Nonetheless, UTIs are common in pregnancy and may increase the risk of adverse pregnancy outcomes.[9] Fosfomycin trometamol has been rated pregnancy category B in the United States, indicating it may be used in pregnancy if clearly needed.[4]

## Side effects

Single 3-gram doses of fosfomycin trometamol are generally well-tolerated.[4,5] Adverse events are transient and tend to resolve spontaneously within one to two days.[4]

Diarrhoea, nausea, and headache are the most frequently reported adverse events.[4,5] Other commonly reported minor adverse events include dizziness, back pain, vaginitis, dysmenorrhoea, abdominal pain, dyspepsia (heartburn, indigestion), pharyngitis, rhinitis, skin rash, pain (non-localised) and asthenia.[5]

## In summary

Fosfomycin is a bactericidal antibiotic with in vitro activity against most urinary tract pathogens.[4] It has emerged as a first-line candidate for single-dose therapy for uncomplicated UTIs in women.[7] In clinical trials in patients with acute uncomplicated lower UTIs, single-dose fosfomycin trometamol was effective and comparable with other antibacterial agents given either as a single-dose or multiple-dose treatments.[4] Resistance to fosfomycin remains low and 97% of *E.coli* isolates from urine in patients with UTIs in South Africa were susceptible to fosfomycin (2021 data).[8] Fosfomycin trometamol is well-tolerated, with a low incidence of adverse events.[4] These comprise mainly gastrointestinal symptoms that are mild, transient and self-limiting.[4]

Fosfomycin trometamol could have an increased role as a therapeutic option against multidrug-resistant community-acquired pathogens.[10] Further research is required to evaluate the potential utility of this agent as a systemic antibiotic.[10]

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