**Fact sheet for professionals**

**Fosfomycin-Trometamol**

*Resistance reduces therapeutic options for urinary tract infections.*

The multidrug resistance problem has arrived in the community setting, where multidrug resistant Escherichia coli are recognised as important causes of hard-to-treat community-acquired urinary tract infections (UTI). The Europe-wide increase of E. coli resistance to all major antimicrobial classes, as detected by the European resistance surveillance system EARS-Net and the ECO·SENS study, is a disturbing development with potentially serious consequences for patients. The speed with which fluoroquinolones as first-line drugs lose their activity against E. coli, the most common pathogen in UTI is without precedent. Not only fluoroquinolone resistance, but also combined resistance to all first-line drugs, is a frequently observed phenomenon that limits therapeutic options and may require parenteral therapy in infections otherwise treatable outside the hospital. These alarming situations raise questions regarding the routine use of the most widely used antibacterial classes (fluoroquinolones, aminopenicillins, cephalosporins, sulfamethoxazole/trimethoprim) as first-line agents for acute uncomplicated UTIs in the community. Resistance threatens the future of currently standard medical treatment for the most common indication for prescribing antimicrobials to women. Some current national guidelines for the therapy of uncomplicated UTI recommend fluoroquinolone-sparing regimens such as fosfomycin-trometamol, nitrofurantoin or pivmecillinam (if available) to reduce the selection pressure for quinolone resistance. Other guidelines call for more current data as information about the optimal drug regimen and duration of therapy is lacking.

*No other choice – Relying on old antibiotics.*

Development of novel antibiotics with activity against relevant multidrug-resistant bacteria causing UTIs is not on the horizon. In situations such as this, physicians increasingly resort to old antibacterial drugs as these drugs may have retained their activity and show no cross-resistance to commonly used antimicrobial classes. However, these old antibiotics have never been characterized using a structured drug assessment process to establish comparative clinical efficacy and effectiveness in randomized controlled trials. A re-evaluation of these drugs is thus urgently needed.

*AIDA studies old drugs to optimize current usage.*

In recognition of the vital nature of these issues, the European Commission has included the characterization of old off-patent antibiotics in their funding scheme for the 7th Framework Program (FP7). One of the work packages of project AIDA (Preserving old antibiotics for the future) aims to compare the clinical effectiveness of nitrofurantoin vs fosfomycin-trometamol (=fosfomycin-tromethamin) for the treatment of lower UTI in adult women at risk of antibiotic-resistant bacteria. Fosfomycin-trometamol as well as nitrofurantoin have unique mechanisms of action, thus, showing no cross-resistance with other classes of antibiotics used for treatment of UTIs. The primary objective of the AIDA open-label randomized clinical trial is to demonstrate the superiority of 5 days of nitrofurantoin over single-dose (3 g) fosfomycin-trometamol for the treatment of lower, uncomplicated UTI in women at risk of antibiotic-resistant pathogens.
**Characteristics of fosfomycin-trometamol**

Fosfomycin has been discovered 45 years ago. It targets the bacterial cell wall by inhibiting the first step of the cell wall synthesis. Fosfomycin disodium is used in several European countries as parenteral last resort drug. The hydrosoluble salt fosfomycin–trometamol allows for an acceptable oral bioavailability. Fosfomycin-trometamol is almost completely excreted by glomerular filtration, and the elimination half life in serum is 5 to 8 h. Due to high concentrations in urine for 24 to 48 hours after administration of a 3g dose, this formulation has been utilized for single-dose therapy of uncomplicated UTIs and is available in most European countries. The antibacterial spectrum of fosfomycin includes the major urinary pathogens such as enterobacteria, staphylococci, and partly Pseudomonas aeruginosa. Fosfomycin–trometamol continues to show a low incidence of E. coli resistant strains (1–3%) worldwide. This drug has retained its activity against quinolone-resistant strains of E. coli and co-resistance with other classes of antibiotics is at present not a problem. According to the ARESC study (Antimicrobial Resistance Epidemiological Survey on Cystitis) fosfomycin retained its activity against E. coli in 98% of the tested strains.

**Clinical usage of fosfomycin-trometamol**

Fosfomycin-trometamol is considered a specialised UTI drug. Several clinical studies showed that a single 3g dose of this drug was effective and comparable with several other antibiotics given either as single-dose or multiple-dose treatments. As high quality conclusive clinical trials are rare concern has been expressed regarding fosfomycin’s ability to achieve full bacterial eradication and the emergence of relapse or re-infection after single-dose fosfomycin-trometamol therapy. Most of the clinical studies have been conducted before the era of high resistance rates against fluoroquinolones and beta-lactam antibiotics. So far, limited clinical data show that fosfomycin-trometamol is effective in the treatment of lower UTI caused by resistant (ESBL-producing) E. coli.

**Safety**

In general, fosfomycin-trometamol is well tolerated and no withdrawals due to adverse events were observed in the clinical studies. Adverse events are usually transient and self-limiting. Gastrointestinal effects, predominantly diarrhea are the most frequently reported adverse events.

**Recommended reading:**