Multidrug resistant urinary tract infections: fosfomycin trometamol

Evidence summary
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nice.org.uk/guidance/esuom17

Key points from the evidence

The content of this evidence summary was up-to-date in July 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

This evidence summary is based on 4 small observational studies. Treatment with fosfomycin trometamol was associated with a clinical success rate (defined as the resolution of symptoms after treatment) of between 77.8% and 94.2% in the 3 studies that reported this outcome. In 2 comparative studies, outcomes were similar in people whose urinary tract infections were treated with fosfomycin trometamol and other antibiotics.

No data on adverse events were available from the studies. More robust studies are needed to further evaluate the safety and efficacy of fosfomycin trometamol for treating urinary tract infections caused by multidrug-resistant bacteria.

Regulatory status: Fosfomycin trometamol (Monuril, Zambon) has a UK marketing authorisation for treating acute lower uncomplicated urinary tract infections. However, it is not distributed in the UK by the holder of the marketing authorisation; it needs to be imported if it is prescribed. Use of imported fosfomycin is unlicensed in the UK.
### Effectiveness
- No statistically significant difference between fosfomycin trometamol and carbapenems in clinical success rates (n=47; 77.8% compared with 95.0%).
- Clinical success rates were similar with fosfomycin trometamol and co-amoxiclav (n=65; 92.9% compared with 83.8%; significance not reported).
- Clinical success occurred in 94.2% of people in 1 case series (n=52).
- A second case series reported microbiological outcomes only (n=41).

### Safety
- Adverse events were not reported in 2 studies; the other 2 studies stated that no adverse events were reported.
- The summary of product characteristics for fosfomycin trometamol states that it is 'generally well tolerated'.
- The most common adverse effects reported are GI disturbances and skin rashes.

### Patient factors
- Fosfomycin trometamol is administered orally.
- The number of doses of fosfomycin trometamol is generally between 1 and 3, which may help some people to adhere to treatment.

### Resource implications
- A single 3 g sachet of fosfomycin trometamol costs £62.10.

### Key points
Fosfomycin trometamol (Monuril, Zambon) is a broad spectrum antibiotic that has a UK marketing authorisation for treating acute lower uncomplicated urinary tract infections. However, fosfomycin is not available commercially as a licensed product in the UK and, currently, the only means of obtaining it is to order from a 'specials' supplier. Brands include Monuril (Zambon; France, Italy and the Netherlands) and Monurol (Pharmazam; Spain and Zambon; USA). Use of these imported products is unlicensed in the UK.

The Management of infection guidance states that, following advice from a microbiologist, fosfomycin or nitrofurantoin should be considered for treating adults with uncomplicated urinary tract infections (no fever or flank pain) due to extended-spectrum beta-lactamase-producing Escherichia coli. If fosfomycin is used, a single 3 g dose is recommended in women. In men, a second 3 g dose should be taken after 3 days.
This evidence summary describes the efficacy and safety of fosfomycin trometamol for treating urinary tract infections caused by multidrug-resistant, including extended-spectrum beta-lactamase-producing, bacteria.

No randomised controlled trials were identified that assessed the clinical efficacy of oral fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria. Four small observational studies were identified that met the inclusion criteria for this evidence review.

The study by Senol et al. (2010) was a small prospective cohort study of 47 people with complicated lower urinary tract infections caused by extended-spectrum beta-lactamase-producing *E. coli* and treated with fosfomycin trometamol or a carbapenem. There was no statistically significant difference between fosfomycin trometamol and carbapenems in terms of clinical and microbiological success rates (77.8% compared with 95.0%, and 59.3% compared with 80.0% respectively).

Rodríguez-Baño et al. (2008) reported outcomes for 65 people with cystitis due to extended-spectrum beta-lactamase-producing *E. coli* which was treated with fosfomycin trometamol or co-amoxiclav. Clinical cure was seen in 92.9% of people taking fosfomycin trometamol and 83.8% of people taking co-amoxiclav; statistical significance was not reported.

The study by Neuner et al. (2012) was a retrospective chart review of 41 people who were in hospital and had a urinary tract infection due to a multidrug-resistant pathogen and who had received fosfomycin trometamol. Microbiological cure occurred in 24 people (58.5%). Clinical success was not reported.

The study by Pullukcu et al. (2007) was a retrospective case series of 52 people with lower urinary tract infections due to extended-spectrum beta-lactamase-producing *E. coli* treated with fosfomycin trometamol. Clinical and microbiological success occurred in 49 people (94.2%) and 41 people (78.8%) respectively.

Adverse events were not reported in 2 studies, and the other 2 studies stated that no adverse events were reported.

Randomised controlled trials of fosfomycin for treating urinary tract infections not specifically due to multidrug-resistant organisms have been carried out. A systematic review and meta-analysis of fosfomycin for cystitis, which included 27 randomised controlled trials, found that fosfomycin was as safe and as effective as other antibiotics (Falagas et al. 2010b). However, this study is not
directly relevant to this evidence summary because it did not specifically assess fosfomycin treating urinary tract infections caused by multidrug-resistant bacteria.

The 4 studies that examined the efficacy and safety of fosfomycin trometamol for treating urinary tract infections caused by multidrug-resistant bacteria were limited by the fact that they were small observational studies. More robust studies are needed to further evaluate the safety and efficacy of fosfomycin for this indication.

Many people in the studies had complicated urinary tract infections and many were in hospital; therefore, care should be taken when applying the results to people with uncomplicated urinary tract infections in the community who are covered by the Management of infection guidance. Similarly, many people took repeated doses of fosfomycin trometamol, rather than a single dose.

About this evidence summary

‘Evidence summaries: unlicensed or off-label medicines’ summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

Overview for healthcare professionals

The Management of infection guidance for primary care for consultation and local adaptation, published by the Health Protection Agency in February 2013, states that fosfomycin (or nitrofurantoin) should be considered on the advice of a microbiologist for treating adults with uncomplicated urinary tract infections (no fever or flank pain) due to extended-spectrum beta-lactamase-producing Escherichia coli.
Regulatory status of fosfomycin

According to the summary of product characteristics, fosfomycin trometamol 3 g (Monuril, Zambon) has a UK marketing authorisation for treating acute lower uncomplicated urinary tract infections caused by pathogens sensitive to fosfomycin.

Fosfomycin is not available commercially as a licensed product in the UK and, currently, the only means of obtaining it is to order from a 'specials' supplier. Brands include Monuril (Zambon; France, Italy and the Netherlands) and Monurol (Pharmazam; Spain and Zambon; USA). Use of these imported products is unlicensed in the UK.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using fosfomycin.

Evidence statements

No randomised controlled trials were identified that assessed the clinical efficacy of oral fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria. Four small observational studies were identified that met the inclusion criteria for this evidence review.

- There was no statistically significant difference between fosfomycin trometamol and carbapenems in terms of clinical and microbiological success rates (77.8% compared with 95.0%, and 59.3% compared with 80.0% respectively) in a small cohort study of 47 people with complicated lower urinary tract infections caused by extended-spectrum beta-lactamase-producing E. coli (Senol et al. 2010).

- In a case–control study, clinical cure rates were similar after treatment with fosfomycin trometamol or co-amoxiclav (92.9% compared with 83.8%) in 65 people with cystitis due to extended-spectrum beta-lactamase-producing E. coli, although statistical significance was not reported (Rodríguez-Baño et al. 2008).

- Microbiological cure occurred in 24 out of 41 (58.5%) people with urinary tract infections due to multidrug-resistant pathogens who had received fosfomycin trometamol in a retrospective chart review (Neuner et al. 2012). Clinical success was not reported.

- Clinical success occurred in 49 out of 52 (94.2%) people in a case series of lower urinary tract infections caused by extended-spectrum beta-lactamase-producing E. coli treated with fosfomycin trometamol (Pullukcu et al. 2007). Microbiological success occurred in 41 out of 52 people (78.8%).
Adverse events were not reported in 2 studies, and the other 2 studies stated that no adverse events were reported.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the Evidence review section.

Efficacy

No randomised controlled trials (RCTs) were identified that assessed the clinical efficacy of oral fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria. Four observational studies were identified that met the inclusion criteria for this evidence review.

Data from 2 of the studies (Rodríguez-Baño et al. 2008 and Pullukcu et al. 2007) were included in a systematic review of fosfomycin for treating multidrug-resistant, including extended-spectrum beta-lactamase-producing, Enterobacteriaceae infections (Falagas et al. 2010a). The systematic review is not discussed in this evidence summary because it provides no relevant additional information. Another systematic review compared fosfomycin with other antibiotics for treating uncomplicated cystitis. This review is not directly relevant to this evidence summary because it does not specifically consider urinary tract infections caused by multidrug-resistant bacteria; however, it has been briefly discussed because it provides some general information on fosfomycin (Falagas et al. 2010b).

Fosfomycin trometamol compared with other antibiotic treatments

The study by Senol et al. (2010) was a small prospective cohort study in 47 adults with complicated lower urinary tract infections caused by extended-spectrum beta-lactamase-producing E. coli who attended a hospital and outpatient clinic in Turkey between March 2005 and January 2006.

The study compared the efficacy of fosfomycin trometamol (n=27; 3 g orally every other night for 3 doses) with the carbapenems (n=20), meropenem (n=12; 1 g intravenously 3 times daily for 14 days) and imipenem cilastatin (n=8; 500 mg intravenously 4 times daily for 14 days). Allocation to treatment was not randomised, and how treatment was decided was not reported.

Reported outcomes were clinical success (defined as resolution of symptoms), microbiological success (defined as sterile urine culture performed 7 to 9 days after the end of treatment), relapse (defined as isolation of extended-spectrum beta-lactamase-producing E. coli in urine cultures
performed 28 to 31 days after the start of treatment), and reinfection (defined as isolation of any pathogen in urine cultures performed 28 to 31 days after the start of treatment).

Clinical and microbiological success rates in the carbapenem and fosfomycin trometamol groups were similar. In the carbapenem group, 19 out of 20 (95.0%) people had clinical success compared with 21 out of 27 (77.8%) in the fosfomycin trometamol group (p>0.05). In the carbapenem group, 16 out of 20 (80.0%) people had microbiological success compared with 16 out of 27 (59.3%) in the fosfomycin trometamol group (p>0.05). The number of people who experienced relapse or reinfection was the same in both groups (each occurred in 1 person receiving fosfomycin trometamol and 1 person receiving a carbapenem). Both reinfections were due to *Klebsiella pneumoniae* (see table 1).

The study by Rodríguez-Baño et al. (2008) was a case–control study of people with community-acquired infections due to (cases), or not due to (controls), extended-spectrum beta-lactamase-producing *E. coli* in 11 Spanish hospitals from February 2002 to May 2003. It investigated the risk factors for all types of community-acquired infections caused by extended-spectrum beta-lactamase-producing *E. coli*. Information on clinical outcomes was reported for 65 people with cystitis due to extended-spectrum beta-lactamase-producing *E. coli* which was treated with either a single 3 g dose of fosfomycin trometamol (n=28) or co-amoxiclav 500 mg/125 mg 3 times daily for 5 to 7 days (n=37).

People were followed for 4 weeks after completion of treatment. They were considered to be clinically cured if they showed no persistent symptoms after completion of treatment and did not experience a recurrence of their urinary tract infection.

Of the people who received fosfomycin trometamol, 26 out of 28 (92.9%) were clinically cured (all isolates were susceptible to fosfomycin). Persistent or recurrent urinary tract infection was microbiologically confirmed in the 2 people in whom treatment failed. Of the people who received co-amoxiclav, 31 out of 37 (83.8%) were clinically cured. In those with susceptible infections (defined as isolates with a minimum inhibitory concentration of 8 micrograms/ml or less), 26 out of 28 (92.9%) were clinically cured. The study did not report whether the difference between the treatments was statistically significant (see table 2).

Table 1 Summary of Senol et al. (2010)
<table>
<thead>
<tr>
<th></th>
<th>Fosfomycin trometamol (one 3 g sachet every other night for 3 doses)</th>
<th>Carbapenems (1 g meropenem IV 3 times daily or 500 mg imipenem cilastatin IV 4 times daily for 14 days)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=27</td>
<td></td>
<td>n=20</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Clinical response/success (resolution of symptoms)</td>
<td>77.8% 21/27</td>
<td>95.0% 19/20</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Microbiological response/success (sterile urine culture performed 7–9 days after the end of treatment)</td>
<td>59.3% 16/27</td>
<td>80.0% 16/20</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Relapse (defined as isolation of ESBL-producing <em>E. coli</em> in urine cultures performed 28–31 days after the start of treatment in people who had previously had microbiological success)</td>
<td>6.3% (1/16)</td>
<td>6.3% (1/16)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Reinfection (defined as isolation of any pathogen in urine cultures performed 28–31 days after the start of treatment in people who had previously had microbiological success)</td>
<td>6.3% (1/16)</td>
<td>6.3% (1/16)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Safety: side effects</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ESBL, extended-spectrum beta-lactamase; *E. coli*, *Escherichia coli*; IV, intravenously; n, number of patients.

Table 2 Summary of Rodríguez-Baño et al. (2008)

<table>
<thead>
<tr>
<th></th>
<th>Fosfomycin trometamol (3 g x 1 dose)</th>
<th>Co-amoxiclav (500 mg/125 mg every 8 hours for 5–7 days)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=28</td>
<td></td>
<td>n=37</td>
<td></td>
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</tbody>
</table>
Clinical cure (no persistent symptomatic or recurrent urinary tract infection)  | 92.9% (26/28)  | 83.8% (31/37)  | Statistical significance of difference not reported

Abbreviations: n, number of patients.

**Fosfomycin trometamol assessed retrospectively in case series**

The study by Neuner et al. (2012) was a retrospective chart review of 41 adults who were in hospital and had a urinary tract infection (abnormal urinalysis and/or symptoms of urinary tract infection) and who had a urine culture for a multidrug-resistant pathogen (defined as resistance to at least 1 agent in 3 or more antimicrobial classes) that was susceptible to, and subsequently treated with, fosfomycin trometamol at a single US centre between January 2006 and December 2010.

This study was uncontrolled. The decision to treat the infection with fosfomycin trometamol was at the discretion of the treating physician. On average, 2.9 fosfomycin doses were given to treat the urinary tract infections. Fosfomycin was given in combination with another antibiotic (tigecycline, aminoglycosides, colistin, pipracillin/tazobactam, imipenem or daptomycin) to 11 people. The primary outcome of this study was overall microbiological cure, defined as the presence of a documented negative urine culture at the end of treatment and/or the absence of relapse or reinfection.

Microbiological cure occurred in 24 people (58.5%); failure was because of either relapse (defined as the development of a urinary tract infection with the same pathogen within 30 days, n=10 [24.4%]) or reinfection (defined as the development of a urinary tract infection with a different organism within 30 days, n=7 [17.1%]).

The study by Pullukcu et al. (2007) was a retrospective case series of 52 adults with lower urinary tract infections due to extended-spectrum beta-lactamase-producing *E. coli* treated with fosfomycin trometamol between September 2004 and July 2006 in an outpatient clinic and hospital in Turkey.

This study was uncontrolled. All people were treated empirically with fosfomycin trometamol (3 g every other night for 3 doses) and had a urine culture performed 7 to 9 days after the end of treatment. The main outcomes were clinical success (defined as resolution of symptoms on a follow-up visit 7 to 9 days after the end of treatment) and microbiological success (defined as a sterile urine culture on follow-up).
Clinical success occurred in 49 people (94.2%) and microbiological success occurred in 41 people (78.8%). Follow-up urine culture was performed 28 days after the end of treatment in 28 of the 41 people with microbiological success. No one experienced a relapse of their infection (defined as isolation of extended spectrum beta-lactamase-producing *E. coli* in the urine cultures performed 28 days after the end of treatment). The rate of reinfection (defined as isolation of any pathogen in the urine cultures performed 28 days after the end of treatment) was 10.7% (3/28).

**Fosfomycin for treating urinary tract infections not specifically caused by multidrug-resistant bacteria**

Falagas et al. (2010b) was a systematic review and meta-analysis that compared fosfomycin with other antibiotics for treating uncomplicated cystitis. It found fosfomycin to be as effective as other antibiotics for treating cystitis. This systematic review is not directly relevant as it did not specifically assess fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria.

**Safety**

The 4 observational studies of fosfomycin trometamol for treating urinary tract infections caused by multidrug-resistant organisms either stated that there were no adverse effects (Senol et al. 2010 and Pullukcu et al. 2007) or did not report adverse events (Neuner et al. 2012 and Rodríguez-Baño et al. 2008).

The systematic review and meta-analysis by Falagas et al. (2010b) that compared fosfomycin with other antibiotics for treating cystitis (not specifically due to multidrug-resistant bacterial infections) found that, compared with other antibiotics, there was no statistically significant difference in the occurrence of adverse events in studies that included only women who were not pregnant (13 RCTs, n=2388) or both men and women who were not pregnant (3 RCTs, n=297). However, fosfomycin was associated with significantly fewer adverse events in pregnant women than other antibiotics (4 RCTs, n=507, relative risk 0.35, 95% confidence interval 0.12 to 0.97). No adverse events were seen in either of the treatment groups in trials involving children.

**Other sources of safety information**

The summary of product characteristics for the 3 g sachets of fosfomycin trometamol (Monuril) that are licensed in the UK states that fosfomycin trometamol is generally well tolerated. Gastrointestinal disturbances (nausea, diarrhoea and heartburn) and skin rashes have been reported. Hypersensitivity reactions, including anaphylaxis, have also been reported rarely.
The label information for the fosfomycin trometamol 3 g preparation (Monurol) that is licensed in the USA states that drug-related adverse events that were reported in more than 1% of people who received fosfomycin during clinical studies included diarrhoea (9.0%), vaginitis (5.5%), nausea (4.1%), headache (3.9%), dizziness (1.3%), asthenia (1.1%) and dyspepsia (1.1%).

Cost

The Management of infection guidance states that fosfomycin or nitrofurantoin should be considered on the advice of a microbiologist for treating adults with uncomplicated urinary tract infections (no fever or flank pain) due to extended-spectrum beta-lactamase-producing E. coli.

The NHS prescription cost analysis for England 2012 reports that each 3 g sachet of fosfomycin trometamol costs £62.10. According to the NHS drug tariff (June 2013), 14 nitrofurantoin 100 mg modified-release capsules cost £5.87.

Relevance to NICE guidance programmes

The use of fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has not produced a clinical guideline on managing urinary tract infections in adults.

NICE has issued a clinical guideline on Urinary tract infection in children: diagnosis, treatment and long-term management (NICE clinical guideline 54). This guideline does not make recommendations for treating urinary tract infections due to multidrug-resistant bacteria in children.

Intervention and alternatives

According to the summary of product characteristics, fosfomycin is a broad-spectrum antibiotic that inhibits bacterial cell wall synthesis. It is active against the pathogens most frequently isolated in urinary tract infections, including those resistant to other antibacterial agents. There is generally no cross-resistance between fosfomycin and other classes of antibacterial agents such as beta-lactams and aminoglycosides.

According to the summary of product characteristics, fosfomycin trometamol (Monuril, Zambon) has UK marketing authorisation for treating acute lower uncomplicated urinary tract infections
caused by pathogens sensitive to fosfomycin. It is also indicated for prophylaxis in diagnostic and surgical transurethral procedures. A single 3 g dose of fosfomycin trometamol is recommended for treating uncomplicated urinary tract infections in adults. A single 2 g dose is recommended for this indication in children.

The Management of infection guidance for primary care for consultation and local adaptation, published by the Health Protection Agency in February 2013, notes that fosfomycin is not available commercially as a licensed product in the UK and, currently, the only means of obtaining it is to order from a 'specials' supplier. Brands include Monuril (Zambon; France, Italy and the Netherlands) and Monurol (Pharmazam; Spain and Zambon; USA). Use of these imported products is unlicensed in the UK.

**Condition**

Urinary tract infections result from the presence and multiplication of microorganisms in 1 or more structures of the urinary tract. Diagnosis of UTI: quick reference guide for primary care, published by the Health Protection Agency in April 2011, lists the following as symptoms of urinary tract infections: dysuria (painful and difficult micturition), increased frequency, polyuria (excessive or abnormally large production or passage of urine), urgency (a strong desire to empty the bladder), suprapubic tenderness and haematuria (blood in the urine).

Urinary tract infections can be subdivided into lower urinary tract infections (for example, cystitis) and upper urinary tract infections (for example, pyelonephritis). They can also be divided into uncomplicated and complicated infections. Uncomplicated infections occur in people with normal urinary tracts and kidney function and are caused by a usual pathogen. Complicated infections are associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that predisposes the person to persistent infection, recurrent infection or treatment failure.

Urinary tract infections can sometimes be caused by bacteria that are resistant to antimicrobial drugs, for example, extended-spectrum beta-lactamase producers. Extended-spectrum beta-lactamase-producing *Escherichia coli* that are resistant to multiple drugs (for example, trimethoprim, penicillins and cephalosporins) are increasing in the community in the UK. (See the Management of infection guidance).
Alternative treatment options

The Management of infection guidance gives treatment options for urinary tract infections in different populations. In adults with uncomplicated urinary tract infection (without fever or flank pain, which may indicate pyelonephritis), urine culture and sensitivity testing should be performed after first-line treatment failure. If the organism is susceptible, amoxicillin is a treatment option. Nitrofurantoin or fosfomycin should be considered on the advice of a microbiologist if the infection is due to multidrug-resistant extended-spectrum beta-lactamase-producing E. coli. If fosfomycin is used, the Management of infection guidance recommends a single 3 g dose in women. In men, a second 3 g dose should be taken after 3 days.

Despite having a UK marketing authorisation, fosfomycin is not currently marketed in the UK and the only means of obtaining it is from a 'specials' supplier. The Management of infection guidance notes that there will be a delay in obtaining the product and careful consideration needs to be given when prescribing and supplying to people who may need treatment more urgently. People should be advised to consult their GP if symptoms worsen while awaiting supply.

Separate recommendations are made in the Management of infection guidance about the treatment of urinary tract infections in pregnant women and children, and prostatitis in men, including second-line treatment options.

Evidence review: efficacy

No randomised controlled trials (RCTs) were identified that assessed the clinical efficacy of oral fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria. Four observational studies were identified that met the inclusion criteria for this evidence review.

Data from 2 of the studies (Rodríguez-Baño et al. 2008 and Pullukcu et al. 2007) were included in a systematic review of fosfomycin for treating multidrug-resistant, including extended-spectrum beta-lactamase-producing, Enterobacteriaceae infections (Falagas et al. 2010a). The systematic review is not discussed in this evidence summary because it provides no relevant additional information. Another systematic review compared fosfomycin with other antibiotics for treating uncomplicated cystitis. This review is not directly relevant to this evidence summary because it does not specifically consider urinary tract infections caused by multidrug-resistant bacteria, however it has been briefly discussed because it provides some general information on fosfomycin (Falagas et al. 2010b).
**Fosfomycin trometamol compared with other antibiotic treatments**

The study by Senol et al. (2010) was a small prospective cohort study in 47 adults with complicated lower urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* who attended a hospital and outpatient clinic in Turkey between March 2005 and January 2006. Complications were the presence of an indwelling urinary catheter, diabetes mellitus, neurogenic bladder, obstruction due to nephrolithiasis, tumour or fibrosis, urinary retention due to benign prostatic hypertrophy, bladder cancer or other urological anatomical abnormalities.

The study compared the efficacy of fosfomycin trometamol (n=27; 3 g orally every other night for 3 doses) with the carbapenems (n=20), meropenem (n=12; 1 g intravenously 3 times daily for 14 days) and imipenem cilastatin (n=8; 500 mg intravenously 4 times daily for 14 days). Reported outcomes were clinical success (defined as resolution of symptoms), microbiological success (defined as sterile urine culture performed 7 to 9 days after the end of treatment), relapse (defined as isolation of extended-spectrum beta-lactamase-producing *E. coli* in urine cultures performed 28 to 31 days after the start of treatment), and reinfection (defined as isolation of any pathogen in urine cultures performed 28 to 31 days after the start of treatment).

Allocation to treatment was not randomised, and how treatment was decided was not reported. All extended-spectrum beta-lactamase-producing *E. coli* were susceptible to carbapenems; however, 1 person who received a carbapenem was infected with a strain that was not susceptible to fosfomycin. It is unclear whether study participants and investigators were blinded to treatment allocation.

The 2 treatment groups were not statistically significantly different in terms of sex, age and complicating factors. About 43% of the study participants were male and their average age was 57.5 years. The most common complicating factor was permanent urinary catheterisation or intermittent clean catheterisation (46.8%). About 76% of people had more than 1 complicating factor; the average number per patient was 2.

Clinical and microbiological success rates in the carbapenem and fosfomycin trometamol groups were similar. In the carbapenem group, 19 out of 20 (95.0%) people had clinical success compared with 21 out of 27 (77.8%) in the fosfomycin trometamol group (p>0.05). In the carbapenem group, 16 out of 20 (80.0%) people had microbiological success compared with 16 out of 27 (59.3%) in the fosfomycin trometamol group (p>0.05). The number of people who experienced relapse or reinfection was the same in both groups (each occurring in 1 person receiving fosfomycin trometamol and 1 person receiving a carbapenem). Both reinfections were due to *Klebsiella pneumoniae*. 
The study by Rodríguez-Baño et al. (2008) was a case–control study of people with community-acquired infections due to (cases), or not due to (controls), extended-spectrum beta-lactamase-producing *E. coli* in 11 Spanish hospitals from February 2002 to May 2003. It investigated the risk factors for all types of community-acquired infections caused by extended-spectrum beta-lactamase-producing *E. coli*. Information on clinical outcomes was reported for 65 people with cystitis due to extended-spectrum beta-lactamase-producing *E. coli* who were treated either with a single 3 g dose of fosfomycin trometamol (n=28) or co-amoxiclav 500 mg/125 mg 3 times daily for 5 to 7 days (n=37).

People were followed for 4 weeks after completing treatment. They were considered to be clinically cured if they showed no persistent symptoms after completing treatment and did not experience a recurrence of their urinary tract infection. It was not reported whether the groups that received the 2 antibiotic regimens for cystitis were similar, and no demographic details or other background information were given. The attending doctor decided on indications for blood cultures, other tests and treatment.

Of the people whose infections were treated with fosfomycin trometamol, 26 out of 28 (92.9%) were clinically cured (all isolates were susceptible to fosfomycin). Persistent or recurrent urinary tract infection was microbiologically confirmed in the 2 people in whom treatment failed.

Of the people whose infections were treated with co-amoxiclav, 31 out of 37 (83.8%) were clinically cured. In those with susceptible infections (defined as isolates with a minimum inhibitory concentration of 8 micrograms/ml or less) 26 out of 28 (92.9%) were clinically cured. The study did not report whether the difference between the treatments was statistically significant.

**Fosfomycin trometamol assessed retrospectively in case series**

The study by Neuner et al. (2012) was a retrospective chart review of 41 adults who were in hospital and had a urinary tract infection (abnormal urinalysis and/or symptoms of urinary tract infection) and who had a urine culture for a multidrug-resistant pathogen (defined as resistance to at least 1 agent in 3 or more antimicrobial classes) that was susceptible to, and subsequently treated with, fosfomycin trometamol at a single US centre between January 2006 and December 2010. The primary outcome of this study was overall microbiological cure, defined as the presence of a documented negative urine culture at the end of treatment and/or the absence of relapse or reinfection.

This study had a retrospective design, was uncontrolled, and reported a single-centre experience of a small number of people. The decision to treat the infection with fosfomycin was at the discretion...
of the treating physician. In addition, the timing of follow-up cultures to assess relapse and reinfection was not standard, although 90% of people had follow-up cultures within 21 days of starting treatment with fosfomycin.

The people in this study were 62 years old on average and 45% were male. The most common comorbidities were diabetes (58.5%), immunosuppression (51.2%), chronic kidney disease (46.3%) and solid organ transplant (36.6%). Thirty-three people (80.5%) had complicated urinary tract infections. The most common complicating factors were use of urinary Foley catheters (63.4%), and history of recurrent urinary tract infections (24.4%). Urine culture identified 44 multidrug-resistant urinary isolates of 8 different pathogens. Susceptibility to fosfomycin was high (only 3 isolates [6.8%] were resistant).

On average, 2.9 fosfomycin doses were given to treat the urinary tract infections. Fosfomycin was given in combination with another antibiotic (tigecycline, aminoglycosides, colistin, pipracillin/tazobactam, imipenem or daptomycin) to 11 people.

Microbiological cure occurred in 24 people (58.5%); failure was because of either relapse (defined as the development of a urinary tract infection with the same pathogen within 30 days, n=10 [24.4%]) or reinfection (defined as the development of a urinary tract infection with a different organism within 30 days, n=7 [17.1%]).

Microbiological cure rates by pathogen were 46% (6/13) for carbapenem-resistant Klebsiella pneumoniae, 38% (3/8) for Pseudomonas aeruginosa, 71% (5/7) for vancomycin-resistant Enterococcus faecium, 57% (4/7) for extended-spectrum beta-lactamase producers, and 100% (9/9) for others.

The study by Pullukcu et al. (2007) was a retrospective case series of 52 adults with lower urinary tract infections due to extended-spectrum beta-lactamase-producing E. coli treated with fosfomycin trometamol between September 2004 and July 2006 in an outpatient clinic and hospital in Turkey. The main outcomes were clinical success (defined as resolution of symptoms on a follow-up visit 7 to 9 days after the end of treatment) and microbiological success (defined as a sterile urine culture on follow-up).

This study had a retrospective design, was uncontrolled, and reported a single-centre experience of a small number of people.

The people included in this study were 55 years old on average and 48% were male. Thirty-six people (69.2%) had complicated urinary tract infections. Complicating factors included indwelling
urinary catheterisation (13.5%), recent urological intervention (11.5%), diabetes mellitus (9.6%) and renal transplantation (9.6%).

All people were treated empirically with fosfomycin trometamol (3 g every other night for 3 doses) and had a urine culture performed 7 to 9 days after the end of treatment.

Clinical success occurred in 49 people (94.2%) and microbiological success occurred in 41 people (78.8%). Follow-up urine culture was performed 28 days after the end of treatment in 28 of the 41 people with microbiological success. No one experienced a relapse of their infection (defined as isolation of extended-spectrum beta-lactamase-producing *E. coli* in the urine cultures performed 28 days after the end of treatment). The rate of reinfection (defined as isolation of any pathogen in the urine cultures performed 28 days after the end of treatment) was 10.7% (3/28).

**Fosfomycin for treating urinary tract infections not specifically caused by multidrug-resistant bacteria**

Fosfomycin has also been used to treat urinary tract infections caused by bacteria that are not multidrug-resistant, including as a first-line treatment. A systematic review and meta-analysis of 27 RCTs (8 double-blind) compared fosfomycin with other antibiotics for treating uncomplicated cystitis (Falagas et al. 2010b).

This study is not directly relevant as it did not specifically assess fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria. Also, it has limitations. For example, there is considerable heterogeneity between the studies, and the quality of many of the included studies is low (10/27 were considered of adequate quality). Nevertheless, the systematic review and meta-analysis does provide some general information of the efficacy of fosfomycin.

All 24 trials in adult populations evaluated a single 3 g dose of fosfomycin. The 3 trials in paediatric populations assessed a single 2 g dose (or 1 g in children aged 1 year or younger in 1 trial). The primary outcome of the meta-analysis was clinical success, defined as the complete cure or improvement of symptoms at the end of treatment.

No statistically significant difference in clinical success was seen between fosfomycin and all comparators combined in trials involving non-pregnant women (10 RCTs, n=1657) or in trials involving men and non-pregnant women (3 RCTs, n=286). Insufficient data were available from trials involving children or pregnant women to perform meta-analyses on clinical success.
No significant difference between fosfomycin and comparators was observed for the secondary outcomes of microbiological success (defined as the presence of a negative urine culture at the end of treatment; data available for all populations), relapse (defined as the detection of the same pathogen as that identified at baseline at long-term follow-up after previous microbiological success; data available for non-pregnant women only) or reinfection (defined as the detection of a different pathogen from that identified at baseline at long-term follow-up, after previous microbiological success; data available for non-pregnant women only).

Evidence review: safety

The 4 observational studies of fosfomycin trometamol for treating urinary tract infections caused by multidrug-resistant organisms either stated that there were no side effects (Senol et al. 2010 and Pullukcu et al. 2007) or did not report adverse events (Neuner et al. 2012 and Rodríguez-Baño et al. 2008).

The systematic review and meta-analysis by Falagas et al. (2010b) that compared fosfomycin with other antibiotics for treating cystitis (not specifically due to multidrug-resistant bacterial infections) found that, compared with other antibiotics, there was no statistically significant difference in the occurrence of adverse events in studies that included only non-pregnant women (13 randomised controlled trials [RCTs], n=2388) or both men and non-pregnant women (3 RCTs, n=297). However, fosfomycin was associated with significantly fewer adverse events in pregnant women than other antibiotics (4 RCTs, n=507, relative risk 0.35, 95% confidence interval 0.12 to 0.97). No adverse events were seen in either of the treatment groups in trials involving children.

Other sources of safety information

The summary of product characteristics for the 3 g sachets of fosfomycin trometamol (Monuril) that are licensed in the UK states that fosfomycin trometamol is generally well tolerated. Gastrointestinal disturbances (nausea, diarrhoea and heartburn) and skin rashes have been reported. Hypersensitivity reactions, including anaphylaxis, have also been reported rarely.

Between 1 July 1963 and 24 April 2013 in the UK there have been 21 adverse drug reaction reports and 1 fatal adverse drug reaction report made to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme including 33 reactions, which may have been related to fosfomycin. Note that 1 report can contain more than 1 adverse drug reaction.
It is important to note that healthcare professionals and patients are asked to report an adverse drug reaction even if they only have a suspicion that the medicine may have caused it. The fact that a report has been submitted does not necessarily mean that the medicine has caused the reaction.

The label information for the fosfomycin trometamol 3 g preparation (Monurol) that is licensed in the USA states that drug-related adverse events that were reported in more than 1% of people who received fosfomycin during clinical studies included diarrhoea (9.0%), vaginitis (5.5%), nausea (4.1%), headache (3.9%), dizziness (1.3%), asthenia (1.1%) and dyspepsia (1.1%).

The label information also states that serious adverse events from the marketing experience with Monurol outside of the USA have been rarely reported and include angioedema, aplastic anaemia, asthma (exacerbation), cholestatic jaundice, hepatitis necrosis, and toxic megacolon. Anaphylaxis and hearing loss have also occurred, although causality has not been established.

Evidence review: economic issues

Cost

No cost-effectiveness studies were identified.

The NHS prescription cost analysis for England 2012 reports that 3 g sachets of fosfomycin trometamol cost £62.10.

The Management of infection guidance for primary care for consultation and local adaptation, published by the Health Protection Agency in February 2013, states that treatment with 100 mg modified-release nitrofurantoin twice daily for 3 days in women and 7 days in men is an option for treating uncomplicated urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in adults with no fever or flank pain. The NHS drug tariff (June 2013) states that 14 nitrofurantoin (100 mg) modified-release capsules cost £5.87.

<table>
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<th>Drug</th>
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<td>£2.52&lt;sup&gt;c&lt;/sup&gt;</td>
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</table>
Current drug usage

The NHS prescription cost analysis for England 2012 reports that 100 community prescriptions for fosfomycin trometamol were dispensed in 2012, costing £12,500 (net ingredient cost). The indications for these fosfomycin prescriptions are not provided.

The Medicines and Healthcare products Regulatory Agency prepares a summary report on the importation of unlicensed medicines. This report details the top 50 products by rank order of the number of notifications of import received (by calendar quarter). Between the start of the third quarter of 2010 and the end of the third quarter of 2011, 87 notifications for fosfomycin sachets and capsules for oral use were received in the third quarter of 2010 and 63 notifications for oral fosfomycin preparations were received in the fourth quarter of 2010. Notifications may have been received in other quarters but not have been within the top 50 products. Notifications were also made for injections, infusions and parenteral preparations. The specific fosfomycin salt ordered and the indications for these fosfomycin imports are not provided.

Evidence strengths and limitations

No randomised controlled trials were identified that assessed the clinical efficacy of oral fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria. Four observational studies were identified that met the inclusion criteria for this evidence review. Of these, 2 had a control group that included people who received a different antibiotic (Senol et al. 2010 and Rodríguez-Baño et al. 2008) and 2 reported results for groups of people who had all been treated with fosfomycin trometamol (Neuner et al. 2012 and Pullukcu et al. 2007). Observational studies are prone to confounding.

The study by Senol et al. (2010) was a small cohort study of 47 adults with complicated lower urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli that were treated with fosfomycin trometamol or a carbapenem. How treatment was decided was not reported. It is unclear whether the study participants and/or the investigator were blinded to treatment allocation.
The study by Rodríguez-Baño et al. (2008) was a case–control study of people with community-acquired infections due to (cases), or not due to (controls), extended-spectrum beta-lactamase-producing *E. coli*. Information relevant to this evidence summary was available for a subset of cases with cystitis due to extended-spectrum beta-lactamase-producing *E. coli*. Cystitis was treated with fosfomycin trometamol or co-amoxiclav. The attending physician decided on indications for blood cultures, other tests and treatment. No demographic details or other background information were provided and it was not reported whether the groups receiving the 2 different antibiotics were similar. The study did not report whether the difference between the treatments was statistically significant.

The study by Neuner et al. (2012) was a retrospective chart review. This study had a retrospective design, was uncontrolled, and reported a single-centre experience of only 41 adults who were in hospital, 80% of whom had complicated urinary tract infections. The decision to treat the infection with fosfomycin trometamol was at the discretion of the treating physician. In addition, the timing of follow-up cultures to assess relapse and reinfection was not standard. This study reported only microbiological, not clinical outcomes.

The study by Pullukcu et al. (2007) also had a retrospective design, was uncontrolled, and reported a single-centre experience of only 52 adults, almost 70% of whom had complicated urinary tract infections.

No studies of fosfomycin for treating urinary tract infections caused by multidrug-resistant bacteria in children or pregnant women were identified.

Three doses of fosfomycin trometamol were taken by most of the people in 3 of the 4 studies (Senol et al. 2010, Neuner et al. 2012 and Pullukcu et al. 2007). For uncomplicated urinary tract infections in adults due to multidrug-resistant extended-spectrum beta-lactamase-producing *E. coli*, Management of infection guidance recommends a single 3 g dose of fosfomycin in women. In men, a second 3 g dose should be taken after 3 days. However, many people in the studies had complicated urinary tract infections and many were in hospital; therefore, care should be taken when applying the results of the studies to people with uncomplicated urinary tract infections in the community who are covered by the Management of infection guidance.

Similarly, the studies included women who were not pregnant and men (average age about 60 years) and the results may not be applicable to children and pregnant women. The Management of infection guidance does not recommend fosfomycin for uncomplicated urinary tract infections in children or pregnant women.
Summary for patients

A summary written for patients is available on the NICE website.

References

Falagas ME, Kastoris AC, Kapaskelis AM et al. (2010a) Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. The Lancet Infectious Diseases 10: 43–50


Health Protection Agency (2013) Management of infection guidance for primary care for consultation and local adaptation [online; accessed 10 June 2013]

Health Protection Agency (2011) Diagnosis of UTI: quick reference guide for primary care [online; accessed 10 June 2013]

Medicines and Healthcare products Regulatory Agency (2013) Drug analysis print fosfomycin [online; accessed 10 June 2013]


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National Health Service (2013) Electronic drug tariff [online; accessed 10 June 2013]


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US Food and Drug Administration (2011) Monurol label [online; accessed 10 June 2013]

Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

1. NICE Evidence
2. NICE
3. Euroscan
4. Broad internet search: Google e.g.: allintitle: Fosfomycin urinary OR cystitis OR pyuria OR bacteriuria filetype:pdf
5. Scirus

MEDLINE & Embase (via Ovid)

Search A

1 Fosfomycin/ (1387)
2 fosfomycin?.tw. (1714)
3 (phosphomycin? or phosphonomycin? or monurol or monuril).tw. (159)
4 23155-02-4.rn. (1387)
5 1 or 2 or 3 or 4 (2110)
Multidrug resistant urinary tract infections: fosfomycin trometamol (ESUOM17)

6 exp Urinary Tract/ (354408)

7 Urinary Tract Infection/ (30788)

8 Bacteriuria/ (6840)

9 Pyuria/ (887)

10 Cystitis/ (6264)

11 (urinary tract infection? or pyuri$ or bacteriuri$ or cystiti$).tw. (36651)

12 6 or 7 or 8 or 9 or 10 or 11 (401242)

13 5 and 12 (421)

14 exp review/ (1776470)

15 (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (74213)

16 ((hand adj2 search$) or (manual$ adj2 search$)).ti,ab,sh. (6401)

17 ((electronic or bibliographic or computeri?ed or online) adj4 database$).ti,ab. (14364)

18 (pooling or pooled or mantel haenszel).ti,ab,sh. (47326)

19 (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (2768)

20 or/15-19 (126424)

21 14 and 20 (56037)

22 Meta Analysis/ (39396)

23 (meta-analy$ or meta analys$ or metaanalys$).ti,ab,sh. (69477)
24 ((systematic$ or quantitativ$ or methodologic$) adj5 (review$ or overview$ or synthesis$)).ti,ab,sh. (56034)

25 (integrative research review$ or research integration).ti,ab,sh. (85)

26 or/22-25 (108144)

27 21 or 26 (136647)

28 clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (242902)

29 (random$ or placebo$ or ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$))).ti,ab,sh. (890703)

30 28 or 29 (989158)

31 (animal$ not human$).sh. (3716929)

32 30 not 31 (882815)

33 (cost$ or economic$).tw. (433329)

34 27 or 32 or 33 (1354297)

35 13 and 34 (112)

36 limit 35 to english language (93)

Search B

1 Fosfomycin/ (1409)

2 fosfomycin?.tw. (1743)

3 (phosphomycin? or phosphonomycin? or monurol or monuril).tw. (163)

4 23155-02-4.rn. (1409)
5 1 or 2 or 3 or 4 (2145)

6 exp Urinary Tract/ (356742)

7 Urinary Tract Infection/ (31075)

8 Bacteriuria/ (6892)

9 Pyuria/ (890)

10 Cystitis/ (6299)

11 (urinary tract infection? or pyuri$ or bacteriuri$ or cystiti$).tw. (37023)

12 6 or 7 or 8 or 9 or 10 or 11 (404025)

13 5 and 12 (428)

14 Epidemiologic studies/ (5724)

15 exp case control studies/ (604734)

16 exp cohort studies/ (1260915)

17 case control.tw. (70499)

18 (cohort adj (study or studies)).tw. (75388)

19 (Follow up adj (study or studies)).tw. (35686)

20 (observational adj (study or studies)).tw. (38798)

21 Longitudinal.tw. (129167)

22 Retrospective.tw. (248189)

23 Cross sectional.tw. (150308)
Multidrug resistant urinary tract infections: fosfomycin trometamol (ESUOM17)

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<td>#3 or #4 3933</td>
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#7 #5 and #6 in Trials 52

**CRD HTA, DARE and EED database**

(Fosfomycin) OR (phosphomycin) OR (phosphonomycin) OR (monurol) OR (monuril) 6

(urinary tract) OR (bacteruria) OR (cystitis) OR (pyuria) 532

#1 AND #2 4

**Grey literature and ongoing trials**

1. FDA
2. EMA
3. MHRA
4. Scottish Medicines Consortium
5. All Wales Medicine Strategy Group
6. metaRegister of Controlled Trials (mRCT)
7. ClinicalTrials.gov

**Manufacturers' websites**

Forest laboratories

Zambon

Inpharzam and Rontag – websites not found

**Evidence selection**

This evidence summary has included clinical trials that have investigated the efficacy of oral fosfomycin for treating multidrug-resistant (including extended-spectrum beta-lactamase producing) urinary tract infections. Studies that have investigated the use of fosfomycin for treating acute urinary tract infections not caused by multidrug-resistant pathogens were excluded.
About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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