Guidelines on the use of oral Fosfomycin 3g sachets for the treatment of multi-resistant urinary tract infections (UTIs)

Background

In recent years there has been a marked increase in the prevalence of UTIs caused by coliforms that are resistant to both penicillins and cephalosporins (i.e. extended spectrum beta lactamase [ESBL] producing organisms). Many of these organisms also carry additional resistance mechanisms which mean all currently available UK licensed oral antibiotics are ineffective.

Multi-resistant coliforms tend to occur in the elderly and in many cases bacteriuria is asymptomatic and does not require antibiotic therapy. However in patients with symptomatic or otherwise clinically significant infection, which may lead to bacteraemia, treatment is indicated. To date these patients have been treated with intravenous therapy, mainly as inpatients or on the Ambulatory Care Unit at the Great Western Hospital in Swindon.

The Health Protection Agency (H.P.A.) now recommends oral Fosfomycin as an alternative agent for treatment of community multi-resistant ESBL UTIs in both males and females (with no fever/flank pain) where microbiological input has been obtained.

Fosfomycin is an orally active, bactericidal, broad spectrum antibiotic that inhibits bacterial cell wall production. It is well absorbed after oral administration and excreted unchanged in the urine. After a 3g dose, very high urine levels are achieved, urine concentrations remaining above the minimum inhibitory concentration of sensitive organisms for up to 48 hours.

Fosfomycin is currently available in most of Europe, Japan and the U.S.A. Although a UK license is held with the MHRA, no UK packaged product is currently available and all supplies must be imported as unlicensed special products.
Prescribing Fosfomycin:

See Appendix 1: The Pathway for the Management of Community-based Patients with non-severe uncomplicated Urinary Tract Infections in whom Fosfomycin and/or a Carbapenem are the only treatment options

Inclusion criteria
Patients are eligible for treatment with Fosfomycin if the following criteria are fulfilled:
- They must be suffering from a symptomatic UTI.
- A urine specimen must have been examined by the laboratory.
- There must be a significant growth of a Fosfomycin-sensitive organism in the sample.
- There must be no other suitable oral treatment alternative, either because of bacterial resistance, or because of patient allergy or intolerance to suitable antimicrobials.

Prescribing information
Dosing: Uncomplicated UTI in females – 1 x 3g sachet on an empty stomach as a single dose
Male patients – 3g sachet, repeated after 48 hours or as advised by microbiology (NB: repeat at 72 hours if CrCl 10 – 50 ml/min)

Contraindications: Known hypersensitivity to fosfomycin or product excipients*
Severe renal insufficiency (CrCl < 10 ml/min), Suspected bacteraemia (NB: NOT recommended for ESBL pyelonephritis or peri-nephric abscess, where alternative I.V. antibiotics are required)

Cautions: Pregnancy and breast feeding

Adverse effects: GI problems e.g. nausea, diarrhoea, headaches, vaginitis, skin rashes (self limiting), rarely hypersensitivity reactions and impairment of liver function

Drug interactions: Metoclopramide slows absorption of Fosfomycin – leave at least 2 – 3 hours between preparations or avoid metoclopramide if possible.

(* due to sucrose content, not recommended in patients with fructose intolerance, glucose–galactose malabsorption syndrome, or sucrase–isomaltase deficiency)

Oral therapy is favourable as it decreases risk for the patient, inconvenience and cost. If a GP has a patient who is potentially eligible for treatment with Fosfomycin they should contact one of the microbiologists to discuss the case. If it is agreed that Fosfomycin would be appropriate, the GP can complete the Fosfomycin Proforma (see Appendix 2) which will also act as the prescription. Producing an FP10 will provide an audit trail in the surgery.

NB. The GP takes full clinical responsibility for the prescribing of an unlicensed medicine with support and advice from Microbiology.

How to obtain Fosfomycin
Oral Fosfomycin is not routinely stocked by community pharmacies. To avoid delays the GWH Pharmacy will hold stock which will be dispensed against a Fosfomycin Proforma on a named-patient basis. The completed Fosfomycin Proforma should be faxed to the GWH dispensary (01793 605021).

The fax should be accompanied by a phone call (Tel: 01793 605024) to agree arrangements for delivery / collection. The fax must be followed by the original in two working days. Pharmacy will dispense the Fosfomycin, which can either be collected by the carer/patient or if necessary dispatched to the GP surgery on the next available transport.
Appendix 1: Pathway for the Management of Community-based Patients with Urinary Tract Infections in whom Fosfomycin and/or a Carbapenem are the only treatment options

Patient with symptomatic UTI due to a multi-resistant gram negative (e.g. ESBL producing organism) in whom no oral agents appear to be available.

Fax completed proforma for 3g stat Fosfomycin to Great Western Hospital Pharmacy on 01793 605021 and telephone 01793 605024 to arrange for patient or representative to collect from GWH or GP surgery (post original proforma to GWH Pharmacy)

Answer to any of these questions is Yes
- is the patient septic? e.g. temp ≥ 38ºC or ≤ 35.5ºC,
- systolic blood pressure <90mmHg, diastolic ≤ 60mmHg, pulse rate >100beats/min
- is the patient confused?
- is the patient dehydrated?
- does the patient have comorbidities that may compromise care at home e.g. renal impairment, diabetes, alcohol excess?
- does the patient have pyelonephritis &/or require urgent inpatient investigations or management e.g. scan?

Is this an uncomplicated UTI due to a Fosfomycin sensitive organism in a woman with no contraindications to Fosfomycin?

Yes
- Consider urgent hospital referral for review and intravenous therapy

No
- Answer to all these questions is No
- Consider a longer Fosfomycin course

Discuss antibiotic options with Microbiologist (01793 604800) ensuring that you mention the following if relevant:
- allergy history
- renal impairment/creatinine clearance
- pregnant, breast feeding
- history of seizures or pre-existing central nervous system disorders
- if taking sodium valproate, oral contraceptive pill, oral anticoagulant or metoclopramide

Prescribe Fosfomycin 3g with review & repeat doses every 48hrs for up to 7 days (every 72 hours if GFR 10 – 50mls/min) Recommended duration is between 3-7 days but depends upon severity and sex of patient. as advised by microbiologist.*

Alternative is IV therapy with Ertapenem or Meropenem dependent on sensitivities

*The current French license for the 3g sachets is for use in women (only) as a single dose for uncomplicated UTIs. However repeated dosing in males is noted in the HPA guidance and accepted off label practice.
### Appendix 2

#### Fosfomycin Proforma

<table>
<thead>
<tr>
<th>GP DETAILS</th>
<th>PATIENT DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of GP</td>
<td>NHS Number</td>
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<tr>
<td>Practice</td>
<td>Patient name</td>
</tr>
<tr>
<td>Practice Address</td>
<td>Patient Address</td>
</tr>
<tr>
<td>Post Code</td>
<td>Patient Post Code</td>
</tr>
<tr>
<td>Date Of Birth</td>
<td>Patient Phone No.</td>
</tr>
</tbody>
</table>

*Fosfomycin is an oral antibiotic (unlicensed in the UK) indicated for the treatment of resistant urinary tract infections. The proforma should be issued only after advice from microbiology has been sought (Tel: 01793 604800)*

1. Does the patient have a **SYMPTOMATIC** UTI? Y / N
2. Has a urine specimen been sent to the laboratory? Y / N
3. Is the cultured organism resistant to all other oral antibiotics, or the patient unable to take these due to intolerance/allergy? Y / N
4. Have you contacted microbiology? Y / N
5. Is there a significant growth of a Fosfomycin-sensitive organism? Y / N
6. Is the patient allergic to fosfomycin? Y / N
7. Does the patient have a creatinine clearance of < 10mls/minute? Y / N
8. Is the patient pregnant / breastfeeding? Y / N

Print name of authorising microbiologist _______________________________________

Please supply:

------ x Fosfomycin 3g sachets

Mix the contents of ONE sachet in half a glass of cold water (approx 100 – 150mls) and take as a single dose (either on an empty stomach or 2 – 3 hours before meals). An ideal time to take it is in the evening before going to bed.

Dose to be repeated after 48 / 72 hours * (*delete as appropriate)

I understand the unlicensed status of the preparation and my responsibilities inherent in its use.

Signed: ____________________________ Date: __________

Print name: ____________________________ Dispensed: __________ Checked: __________ Date: __________

Please indicate route of supply to patient by ticking the relevant box

| Dispersed prescription to be sent to practice on first available transport from GWH for patient/ representative to collect (confirm with dispensary on telephone number below) |
| Dispersed prescription to be collected from GWH Pharmacy by patient or patient representative |

Fax proforma to GWH Pharmacy 01793 605021, then confirm delivery tel: 01793 605024. Once faxed, original to be sent by post to GWH Pharmacy, Marlborough Rd, Swindon, SN3 6BB.