REVIEW ARTICLE

Journal of Pre-Clinical and Clinical Research, 2014, Vol 8, No 2, 51-54
www.jpccr.eu

Fosfomycin as an alternative therapeutic option for treatment of infections caused by multi-resistant Gram-negative bacteria

Magdalena Zdziebło[1], Sylwia Andrzejczuk[1], Beata Chudzik-Rząd[1], Marek Juda[1], Anna Malm[1]

[1] *Department of Pharmaceutical Microbiology with Laboratory for Microbiological Diagnostics, Medical University of Lublin, Poland*

Zdziebło M, Andrzejczuk S, Chudzik-Rząd B, Juda M, Malm A. Fosfomycin as an alternative therapeutic option for treatment of infections caused by multi-resistant Gram-negative bacteria. J Pre-Clin Clin Res. 2014; 8(2): 51–54. doi: 10.5604/18982395.1135649

Abstract

The problem of significantly reduced drug use concerns particularly the infections caused by multi-resistant pathogens, especially Gram-negative bacteria. In this regard, interest is increasing in the known for nearly 50 years, but now frequently forgotten antibiotic – fosfomycin. Fosfomycin possesses high effectiveness for multidrug-resistant bacteria, comprising of extended-spectrum β-lactamases (ESBL), *Klebsiella pneumoniae* carbapenemases (KPC); commonly, the pandrug-resistant (PDR) and the extensively drug-resistant (XDR) strains, especially from *Enterobacteriaceae* family. Because of facilitated distribution into inflamed tissues and a very broad range of *in vitro* bactericidal activity, fosfomycin may have various applications in the treatment of many kinds of bacterial infections, including acute uncomplicated infections of the urinary bladder or complicated urinary tract infections, urinary tract sepsis, pyelonephritis, cystitis, prostatitis and chronic lung infections in patients with cystic fibrosis, the great majority caused by multi-resistant Gram-negative bacteria, and in the therapy eradicating multidrug-resistant *Helicobacter pylori*. Fosfomycin may limit the toxicity of other antibiotics and play a protective role in the process of bacterial resistance development during the therapy. Combinations of different antimicrobials enable the use of forgotten antibiotics in commonly occurring infections, although they are still completely incurable.

Key words

fosfomycin, multidrug-resistant bacteria, urinary tract infections, prostatitis, cystic fibrosis

INTRODUCTION

The problem of significantly reduced drug use concerns particularly infections caused by multidrug-resistant pathogens (MDR), especially Gram-negative bacteria [1]. For such infections, one or two antibiotics are the only treatment option, often with contracted indications for use (side-effects, pending primary diseases, other taints). Even though there are so many types of antibiotics with a wide range of activities, widespread availability contributed to the general abuse in therapy. Therefore, multidirectional actions to reintroduce the activity of such commonly called 'old' antibiotics, and enhance the effectiveness of clinical treatment, and in that way are being taken worldwide [2]. The main issue is retrospection into the principal and basic knowledge about interactions antibiotic-microorganism, as well as to keep track of rapid changes in bacteria susceptibility to many antibiotics and the emergence of new mechanisms of drug resistance. In this regard, interest is increasing in the known for nearly 50 years, but now frequently forgotten antibiotic – fosfomycin.

General features of fosfomycin. Fosfomycin (FOS), originally named fosfonomycin, was discovered in Spain in 1969 in the actinomycetes *Streptomyces freundii* culture [3]. FOS, a derivative of the phosphonic acid, with a specific epoxide ring, is not classified into any of the known groups of antimicrobial agents. The lowest molecular weight gives it the possibility for rapid diffusion and penetration into many tissues of the human body, including the blood-brain barrier, where it reaches maximum therapeutic concentrations [4].

Nowadays, fosfomycin occurs in three pharmaceutical forms: two orally dispensed (pessaries for solution preparing) fosfomycin with tromethamine (commonly known as trometamol), available in Poland, and calcium fosfomycin, as well as fosfomycin disodium capsules applied by intravenous infusions [5]. It is a cell-wall active antimicrobial agent, primarily inhibiting the first step of the murein/peptidoglycan synthesis (a condensation of the UDP-N-acetylglucosamine and the phosphoenolpyruvate) through close binding to the bacterial pyruvate transferase. As a result, conversion into the UDP-N-acetylmuramine acid (UDP-MurNAc) – cell wall component protein – becomes impossible [6]. FOS also inhibits the adhesion of uropathogenic bacteria to urothelium. This is probably result of limiting the fusion of the oligomannose from bacterial cell walls to the surroundings (e.g. the mucous membrane of the urinary tract) allowing the removal of pathogens along within urine [7]. It is commonly used in the treatment of uncomplicated and complicated urinary tract infections UTIs.

Fosfomycin activity against multidrug-resistant pathogens. It is a promising fact that most of the ESBL-producing multidrug-resistant *Enterobacteriaceae* strains are susceptible to fosfomycin, which Falagas et al. [8] and Gupta et al. [9] have widely presented.

In the first reviewed studies, most of the identified ESBL-producing *Enterobacteriaceae* isolates were *Escherichia coli* or *K. pneumoniae*. All confirmed isolates were specifically

Address for correspondence: Sylwia Andrzejczuk, Department of Pharmaceutical Microbiology with Laboratory for Microbiological Diagnostics, Medical University of Lublin, 20-059 Lublin, Poland
E-mail: sylwia.andrzejczuk@umlub.pl

Received: 09 September 2014; accepted: 18 November 2014

susceptible to fosfomycin in the range of 90–100% and 80–90%, respectively [8]. Secondly, among 150 *E. coli* clinical isolates, over 52% of the strains were ESBL-producers, and 8% were reported as AmpC-type β-lactamases-producing strains. All strains were identified as fosfomycin susceptible. Due to the limited choice of antimicrobial agents in the treatment of UTIs caused by ESBL-producing bacteria, and the barely noticeable resistance rate against FOS, authors recommend its use as an alternative drug for uncomplicated UTIs [9]. In a Spanish multicentre study, the authors closely analyzed the resistance rate of ESBL *E. coli* isolates. In 2009, total resistance was estimated at the low level of 3%, but its significant increase over the five previous years was also observed (from 4% in 2005 to 11.4% in 2009). This sudden increase was probably associated with the rapid rise of fosfomycin use in the community [10], which is in accordance with the studies by Oteo et al. [11]. The authors described a nearly 50% intensification of community consumption of FOS, and an unexpected extension of resistance in ESBL-positive (CTX-M-14) *E. coli* clinical strains from 2.2% to 21.7% in Spain in 2004–2008. A similar study on CTX-M-15-producing *E. coli* strains investigated a combination of FOS-cefoxitin for the treatment of UTIs. A bacterial resistance development was obtained *in vitro* at 24 hours when fosfomycin and cefoxitin were used in monotherapy in a concentrations of 4xMIC. The results of *in vivo* experiments in a murine model indicated that the fosfomycin-cefoxitin combination had efficient bactericidal activity and caused kidneys sterilization. For this reason, that combination of antimicrobial agents may be successfully applied in a treatment of UTIs due to ESBL-producing *E. coli* [12]. Furthermore, Pontikis et al. [13] showed *in vivo* activity of FOS against the XDR and PDR strains. In a group of 26 patients, 2 described isolates were carbapenemases-producing XDR *K. pneumoniae* and 15 PDR. In turn, from 17 identified *Pseudomonas aeruginosa* strains, 16 were registered as an XDR and 1 as a PDR. All examined individuals were critically ill patients in the Greek intensive care units (ICUs), mostly suffering from mono- or poly-microbial primary bacteraemia, ventilator-associated pneumonia (VAP) and catheter-related bloodstream infections. Fosfomycin and other combination therapy brought a clinical cure in nearly 55% of cases. Complete bacterial eradication was noted in 56% and mortality rate reached only 40% of patients. During the therapy, a resistance to fosfomycin developed in almost 3 cases, with the minimal inhibitory concentration (MIC) value reaching from 16–32 g/mL to over 256 g/mL. All these results may suggest that fosfomycin administered in monotherapy or in a combination with other antibiotics (colistin, tigecycline, gentamicin, meropenem and piperacillin/tazobactam) could be a good alternative for the infections caused by XDR or PDR strains, but this requires further research.

Therapeutic applications of fosfomycin. A high bioavailability in the human body is decidedly the most advantageous feature of fosfomycin. Significantly high concentrations are mostly achieved in the serum (lack of interactions with plasma proteins). Furthermore, the antibiotic proves a good distribution into the soft tissues, lungs, bones, heart valves, urinary bladder, prostate and seminal vesicles [4]. Additionally, it passes through the blood-brain barrier, reaching clinically high levels in the cerebro-spinal fluid (CSF), where, however, its activity against Gram-negative bacteria is apparently diminished [2, 5]. FOS also highly penetrates purulent lesions, and in almost 95% is excreted unchanged with the urine within 24 hours [5, 6].

Table 1. Antimicrobial activity of fosfomycin against Gram-negative bacteria

Spectrum of activity	Citation
Escherichia coli	2, 14
ESBL *E. coli* (CTX-M-14,15)	11, 15, 16, 17
Proteus mirabilis	5
Enterobacter spp.	5
Citrobacter spp.	5
Serratia marcescens	4
Neisseria meningitidis	5
Shigella spp.	5
Salmonella typhi	5
KPC, ESBL, XDR, PDR *Klebsiella pneumoniae*	2, 8, 13, 16, 18
Acinetobacter baumannii	20
MDR *A. baumannii*	18
Pseudomonas aeruginosa	2, 4, 19
MDR, XDR, PDR *P. aeruginosa*	6, 8, 18, 13, 20, 21

Because of facilitated distribution into inflamed tissues and a very broad range of *in vitro* bactericidal activity (Tab. 1), fosfomycin may have various applications in the treatment of many kinds of inflammations. FOS is commonly administered in female acute uncomplicated urinary bladder infections and pyelonephritis [22], or uncomplicated urinary tract infections (UTIs) [2, 23]. It is also widely recommended for the UTIs treatment (also administered to pregnant women under strict medical control), and protectively in medical interventions within the urinary tract when caused by the most common uropathogens, comprising of *Klebsiella pneumoniae* carbapenemases (KPC) and multi-drug resistant *P. aeruginosa*. Fosfomycin is a so-called 'urodesinfectant drug' of proven bactericide effect, and its potential to eradicate the UTIs pathogens reaches even 80–99% [7, 24]. The Food and Drug Administration (FDA) in the USA recommends fosfomycin-trometamol only in therapy for uncomplicated infections of the urinary bladder (cystitis) [4]. At the same time, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland allowed its use for the therapy of uncomplicated abundant bacteriuria, in a prevention of UTIs associated with surgical and transurethral diagnostic procedures [25].

FOS may also be of major importance in bacterial prostatitis, closely associated with UTIs infection. Until now, there has been no study conducted on the use of FOS and testing its accurate penetration into the prostate tissue. One of the latest researches examined a group of healthy males undergoing transurethral resection of the prostate who were treated with a single 3 g dose of oral fosfomycin tromethamine as a presurgical prophylaxis. The authors achieved satisfying concentrations of fosfomycin in most cases (with therapeutic concentrations detectable up to 17 hours). They also suggest the possibility to use it in patients with urinary tract sepsis and prostatitis due to MDR Gram-negative bacteria. Unfortunately, the authors have not investigated any antimicrobial susceptibility, or any impact

of the fosfomycin on the minimal inhibitory concentration (MIC) value [26].

There are also proposals to introduce FOS into the antibiotic therapy of Gram-negative pneumonia in patients on mechanical ventilation. A phase 1 randomized and double-blind study has evaluated the safety of 50 mg/mL amikacin and 20 mg/mL fosfomycin solution in ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP). The authors demonstrated that following administration, fosfomycin was rapidly absorbed and the treatment was well tolerated and safe. A second part of the clinical studies has been initiated and will consider the usefulness of 300/120 mg amikacin/fosfomycin intravenous doses as therapy in patients on mechanical ventilation against Gram-negative bacteria [27].

Due to the increasing resistance to commonly used treatment against MDR *Helicobacter pylori* in some countries, there is a growing need for new drugs or combinations. The authors considered the use of a regimen of rifampin or fosfomycin to eradicate that pathogen. Overall resistance rate to fosfomycin reached 8.3%, and MIC_{90} values were also much lower than commonly used agents (metronidazole, clarithromycin, levofloxacin). This indicates the important role of fosfomycin in eradication therapy of *H. pylori* [28]. These data are in accordance with earlier results [29]. The authors found that from 10 confirmed multi-drug resistant *H. pylori* isolates, all strains were susceptible to FOS. For that reason, it was decided to change the classical empirical treatment to a therapy containing a proton-pump inhibitor, tetracycline, bismuth subsalicylate and fosfomycin as a second-line rescue. With this, the *H. pylori* eradication was achieved in 95% of patients. These studies indicate a promising role of FOS as a part of empirical second-line MDR *H. pylori* infections treatment, especially in countries with a high prevalence of resistance to metronidazole, which requires larger controlled trials.

Apart from the very expensive process of developing new antibiotics, scientists are constantly trying to modify well-known drugs to facilitate application and multiply their effectiveness. A combination with other antibiotics, such as β-lactams or aminoglycosides, expands the activity of fosfomycin to *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [8]. For that reason, it has been successfully introduced into therapy for respiratory infections, such as pneumonia [5] and cystic fibrosis (CF) [6]. A very rewarding improvement has been achieved in spirometry results. No influence was observed on renal function, and surprisingly, only occasional side-effects when the combination therapy was used in patients with cystic fibrosis, co-infected by *P. aeruginosa* MDR strains (the most important pathogen colonizing respiratory tract in 80% of cases) [6, 30].

Due to no satisfactory efficacy in monotherapy being achieved, an attempt is currently being made to associate fosfomycin with tobramycin (TOB) at a 4:1 (wt/wt) ratio – both being inhaled. MacLeod et al. compared *in vitro* and *in vivo* activities of the fosfomycin/tobramycin combination with those of FOS and TOB alone, against pathogens involving cystic fibrosis and non-CF bronchiectasis. The authors have noted the absence on pharmaceutical market of any fosfomycin aerosol formulation deliverable directly to the lungs. They observed strong FOS activity against *E. coli* and *Klebsiella* spp. strains and moderate potential to eradicate *P. aeruginosa*. However, the FOS/TOB regimen resulted in a rapid bactericidal effect against Gram-negative bacteria. All these outcomes suggest that fosfomycin/tobramycin should be investigated further as a novel treatment option for bronchiectasis CF and non-CF infections [31]. In a study on patients from more than 30 centres involved in cystic fibrosis therapy in 2008–2010, fosfomycin/tobramycin inhalation was used in 2 doses: 80/20 mg and 160/40 mg. It was assessed that both doses of antibiotics significantly increased spirometric indices, compared with the cycle of inhaled aztreonam. Two-component FOS/TOB therapy was well tolerated, and a 80/20 mg dose showed fewer side-effects. Moreover, the density of *P. aeruginosa* colonies was significantly reduced in patients co-infected with the *methicillin-resistant Staphylococcus aureus* (MRSA). This recommends the use of that dose for further clinical studies [21]. Despite such satisfactory clinical results, the Polish Society Against Cystic Fibrosis, a member of the Cystic Fibrosis Worldwide, still recommends standard therapy comprising tobramycin, colistin (for economic reasons and due to rare resistance induction) and aztreonam. For the same issues, in some countries (Poland and the United Kingdom) colistin is the first-line antibiotic in CF patients with chronic lung infections caused in the great majority by *P. aeruginosa* [30].

An important aspect is the fosfomycin activity against biofilm, particularly formed by *P. aeruginosa* [5]. Monotherapy studies in animal models showed that fosfomycin had the strongest eradication activity for *E. coli* biofilm among all used antibiotics [17]. This agent probably enhances the activity and penetration of other antibiotics inside the biofilm, which may be associated with the unique mechanism of action of fosfomycin [5]. The additive synergism was found in the combination of fosfomycin with fluoroquinolones (ciprofloxacin, ofloxacin), polymyxins (colistin), carbapenems (imipenem, meropenem, doripenem), aminoglycosides (netilmicin), and cotrimoxazole (trimethoprim/sulfamethoxazole) [16, 17]. The combination with tigecycline effectively removed the *E. coli* biofilm structure in 25%, and the highest efficiency was achieved in a combination with colistine, which showed a cure rate of up to 70% of all treatment regimens. Fosfomycin was the only single antimicrobial agent which was able to eradicate *E. coli* biofilms (cure in 17% of cases). A combination of colistin-tigecycline (50%) and fosfomycin-gentamicin (42%) cured significantly more infected cases than colistin-gentamicin (33%) or fosfomycin-tigecycline (25%) ($p<0.05$). The combination of fosfomycin-colistin showed the highest cure rate (67%), which was significantly better than fosfomycin alone. This suggests a high probability of effectiveness in the treatment of infections associated with the insertion of implants (implant-associated infections) as a result of colonization by the Gram-negative bacteria [17]. The combination of fosfomycin with carbapenems reached nearly 70% of synergistic action, especially in relation to KPC. This was probably caused by the independent mechanisms of action and separate points of the molecular target. The authors also suggest that three-component antibiotic therapy with fosfomycin can bring satisfying results, because fosfomycin – as a relatively safe drug – may limit the toxicity of other antibiotics, such as aminoglycosides nephrotoxicity [16]. Moreover, similar antibiotic combinations have medical implications, they play a protective role and prevent the development of bacterial resistance against FOS during the therapy, and enhance the *in vivo* activity of fosfomycin [32].

CONCLUSIONS

The treatment of infections caused by the MDR, PDR, or even XDR pathogens, is an important clinical problem. An increase in antimicrobial resistance impedes effective therapy. Nowadays, there is a tendency to reduce the application of standard antibiotics, particularly in monotherapy. For that reason, scientists are attempting to associate the 'old' antibiotics with others, and broaden their spectrum of activity in the multidrug-resistant infections treatment. In this way, the adverse effects of certain antibacterial agents (e.g. toxicity) are strongly reduced. Combinations of different antimicrobials enable the use of forgotten antibiotics in commonly occurring infections which are still completely incurable. In this regard, the main advantages of fosfomycin comprise of nontoxicity, easy dosages, good penetration into many tissues, and little ability to display cross-resistance to other antibiotics, as well as bacterial low resistance development. All of which indicates that fosfomycin becomes an important alternative drug for various infections caused by multidrug-resistant pathogens.

REFERENCES

1. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012; 18(3): 268–281.
2. Bergen PJ, Landersdorfer CB, Lee HJ, Li J, Nation RL. 'Old' antibiotics for emerging multidrug-resistant bacteria. Curr Opin Infect Dis. 2012; 25(6): 626–633.
3. Hendlin D, Stapley EO, Jackson M, Wallick H, Miller AK, Wolf FJ, Miller TW, Chaiet L, Kahan FM, Foltz EL, Woodruff HB, Mata JM, Hernandez S, Mochales S. Phosphonomycin, a new antibiotic produced by strains of Streptomyces. Science. 1969; 166: 122–123.
4. Raz R. Fosfomycin: an old-new antibiotic. Clin Microbiol Infect. 2012; 18: 4–7.
5. Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. Int J Infect Dis. 2011; 15(11): 732–739.
6. Mirakhur A, Gallagher MJ, Ledson MJ, Hart CA, Walshaw MJ. Fosfomycin therapy for multiresistant Pseudomonas aeruginosa in cystic fibrosis. J Cyst Fibros. 2003; 2(1): 19–24.
7. Jóźwik M. Skuteczność lecznicza preparatu MONURAL® w zwalczaniu zakażeń układu moczowego u kobiet. Gin Prakt. 2005; 87(6): 24–28 (in Polish).
8. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis. 2010; 10(1): 43–50.
9. Gupta V, Rani H, Singla N, Kaistha N, Chander J. Determination of extended-spectrum β-lactamases and AmpC production in uropathogenic isolates of *Escherichia coli* and susceptibility to fosfomycin. J Lab Physicians. 2013; 5(2): 90–93.
10. Oteo J, Bautista V, Lara N, Cuevas O, Arroyo M, Fernández S, Lázaro E, de Abajo FJ, Campos J. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*. J Antimicrob Chemother. 2010; 65(11): 2459–2463.
11. Oteo J, Orden B, Bautista V, Cuevas O, Arroyo M, Martinez-Ruiz R, Perez-Vazquez M, Alcaraz M, Garcia-Cobos S, Campos J. CTX-M-15-producing urinary Escherichia coli O25b-ST131-phylogroup B2 has acquired resistance to fosfomycin. J Antimicrob Chemother. 2009; 64(4): 712–717.
12. Lefort A, Chau F, Lepeule R, Dubée V, Kitzis MD, Dion S, Fantin B. Activity of fosfomycin alone or combined with cefoxitin in vitro and in vivo in a murine model of urinary tract infection due to Escherichia coli harbouring CTX-M-15-type extended-spectrum β-lactamase. Int J Antimicrob Agents. 2014; 43(4): 366–369.
13. Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, Oikonomou A, Poulakou G, Roilides E, Giamarellou H. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. Int J Antimicrob Agents. 2014; 43(1): 52–59.
14. Ho PL, Chan J, Lo WU, Lai EL, Cheung YY, Lau TC, Chow KH. Prevalence and molecular epidemiology of plasmid-mediated fosfomycin resistance genes among blood and urinary Escherichia coli isolates. J Med Microbiol. 2013; 62(11): 1707–1713.
15. Tullio V, Cuffini AM, Banche G, Mandras N, Allizond V, Roana J, Giacchino F, Bonello F, Ungheri D, Carlone NA. Role of fosfomycin tromethamine in modulating non-specific defence mechanisms in chronic uremic patients towards ESBL-producing Escherichia coli. Int J Immunopathol Pharmacol. 2008; 21(1):153–160.
16. Samonis G, Maraki S, Karageorgopoulos DE, Vouloumanou EK, Falagas ME. Synergy of fosfomycin with carbapenems, colistin, netilmicin, and tigecycline against multidrug-resistant Klebsiella pneumoniae, Escherichia coli, and Pseudomonas aeruginosa clinical isolates. Eur J Clin Microbiol Infect Dis. 2012; 31(5): 695–701.
17. Corvec S, Furustrand TU, Betrisey B, Borens O, Trampuz A. Activity of fosfomycin, tigecycline, colistin and gentamicin against extended spectrum beta-lactamase-producing *E. coli* in a foreign-body infection model. Antimicrob Agents Chemother. 2013; 57(3): 1421–1427.
18. Giamarellou H, Poulakou G. Multidrug-resistant Gram-negative infections: what are the treatment options? Drugs. 2009; 69(14): 1879–1901.
19. Kastoris AC, Rafailidis PI, Vouloumanou EK, Gkegkes ID, Falagas ME. Synergy of fosfomycin with other antibiotics for Gram-positive and Gram-negative bacteria. Eur J Clin Pharmacol. 2010; 66(4): 359–368.
20. Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant Gram-negative organisms: extended-spectrum β-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae and multi-resistant Pseudomonas aeruginosa. Mayo Clin Proc. 2011; 86(3): 250–259.
21. Trapnell BC, McColley SA, Kissner DG, Rolfe MW, Rosen JM, McKevitt M, Moorehead L, Montgomery AB, Geller DE. Fosfomycin/tobramycin for inhalation in patients with cystic fibrosis with pseudomonas airway infection. Am J Respir Crit Care Med. 2012; 185(2): 171–178.
22. UpToDate: Fosfomycin Drug Information. 2011. Available at: http://www.uptodate.com.contents.fosfomycin-drug-information (accessed: 2014.07.12).
23. Schito GC. Why fosfomycin trometamol as first line therapy for uncomplicated UTI? Int J Antimicrob Agents. 2003; 22(Suppl 2): 79–83.
24. Neuner EA, Sekeres J, Hall GS, van Duin D. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. Antimicrob Agents Chemoter. 2012; 56(11): 5744–5748.
25. The Office for Registration of Medical Products, Medical Devices and Biocidal Products. en.urpl.gov.pl
26. Gardiner BJ, Mahony AA, Ellis AG, Lawrentschuk N, Bolton DM, Zeglinski PT, Frauman AG, Grayson ML. Is fosfomycin a potential treatment alternative for multidrug-resistant Gram-negative prostatitis? Clin Infect Dis. 2014; 58(4): 101–105.
27. Montgomery AB, Vallance S, Abuan T, Tservistas M, Davies A. A randomized double-blind placebo-controlled dose-escalation phase 1 study of aerosolized amikacin and fosfomycin delivered via the PARI investigational eFlow® Inline Nebulizer System in mechanically ventilated patients. J Aerosol Med Pulm Drug Deliv. 2014; 27(6): 441–448.
28. Boyanova L, Davidkov L, Gergova G, Kandilarov N, Evstatiev I, Panteleeva E, Mitov I. Helicobacter pylori susceptibility to fosfomycin, rifampin, and 5 usual antibiotics for H. pylori eradication. Diagn Microbiol Infect Dis. 2014; 79(3): 358–361.
29. Barahona-Garrido J, Quiñonez NF, Cerda-Contreras E, Maria Sarti H, Téllez-Ávila FI. Fosfomycin-containing second-line treatment for Helicobacter pylori infection. Am J Gastroenterol. 2013;108(5): 858–859.
30. Polskie Towarzystwo Walki z Mukowiscydozą [Polish Association for Mucoviscidosis Control] http://www.ptwm.org.pl/ (access: 2014.01.07) (in Polish).
31. MacLeod DL, Barker LM, Sutherland JL, Moss SC, Gurgel JL, Kenney TF, Burns JL, Baker WR. Antibacterial activities of a fosfomycin/tobramycin combination: a novel inhaled antibiotic for bronchiectasis. J Antimicrob Chemother. 2009; 64(4): 829–836.
32. Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? Eur J Clin Microbiol Infect Dis. 2010; 29(2): 127–142.