

Bölüm 4

FOSFOMİSİN

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GİRİŞ

Son yıllarda çoklu ilaca dirençli (Multiple drug resistance: MDR) veya aşırı derecede ilaca dirençli (Extensive drug resistance: XDR) patojenlerin yayılması, bunların sebep olduğu enfeksiyonların tedavisini çok zor bir hale getirmiştir ve bu enfeksiyonlarda kullanılan antibiyotik tedavisinin yeniden düzenlenmesini gereklilikmiştir. Sonuç olarak tedavi için eski antibiyotiklere yönelik olmuştur. Fosfomisin de bunlardan biridir. Fosfomisin bakterisidal etkili, düşük moleküller ağırlığa sahip, hücre duvar sentezini inhibe eden, geniş spektruma sahip bir antibiyotiktir. Oral ve intravenöz (iv) formunun olması, oral formunun tek doz olarak kullanılabilmesi ve buna bağlı olarak hasta uyumunun daha iyi olması, diğer antimikrobiyal ajanlar ile çapraz direncin az olması, şu an için çok yüksek olmayan direnç oranları, tolerabilitesinin yüksek olması, yan etkilerinin az olması nedeniyle, fosfomisin uygun enfeksiyonlarda tercih edilebilecek bir ajan olarak karşımıza çıkmaktadır.

KÖKENİ, KİMYASAL YAPISI

Fosfomisin, orijinal ismi fosfonomisin olan ilaç, ilk defa 1969 yılında *Streptomyces fradiae* (ATCC 21096) türünden fermentasyon ile elde edilmiş olan (ayrıca *S. wedmorensis* (ATCC 21239)

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TOLERABİLİTE VE YAN ETKİLER

Fosfomisin için hafif, kendi kendini sınırlayan gastrointestinal rahatsızlıklar, genellikle ishal, en sık bildirilen yan etkilerdir, bunun yanında daha nadir olarak deri ve deri altı dokulara ait yan etkiler görülmüştür (85,86). Belirtilen tüm yan etkilerin genellikle çok ağır olmadığı, hafif düzeyde oldukları ve fosfomisin ilaç olarak genellikle iyi tolere edildiği belirtilmektedir. Diğer yaygın ancak küçük yan etkiler baş dönmesi, baş ağrısı ve vajinitittir. Japonya'da 6 yıllık bir dönemde 35.481 hastayı içeren bir pazarlama sonrası çalışmada sadece bir psödomembranöz kolit vakası kaydedilmiştir (87).

KAYNAKLAR

1. Hendlin D, Stapley EO, Jackson M, et al. Phosphonomycin, a new antibiotic produced by strains of *Sreptomyces*. Science 1969;166(3901):122–123.
2. Falagas ME, Giannopoulou KP, Kokolakis GN and et al. Fosfomycin: use beyond urinary tract and gastrointestinal infections. Clin Infect Dis. 2008;46(7):1069–1077. Doi: 10.1086/527442.
3. Frimodt-Møller N. 2010. Fosfomycin, In Grayson ML (ed), Kucers' The use of antibiotics, 6th ed. Edward Arnold Ltd, London (p 935–944). United Kingdom.
4. Popovic M, Steinort D, Pillai S, et al. Fosfomycin: An old, new friend? Eur. J. Clin. Microbiol. Infect. Dis. 2010;29(2):127–142. Doi: 10.1007/s10096-009-0833-2.
5. Kahan FM, Kahan JS, Cassidy PJ and et al. The mechanism of action of fosfomycin (phosphomycin). Ann NY Acad Sci 1974;235(0):364–86. Doi: 10.1111/j.1749-6632.1974.tb43277.x
6. Eschenburg S, Priestman M, Schonbrunn E. Evidence that the fosfomycin target Cys115 in UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) is essential for product release. J Biol Chem 2005; 280(5): 3757–3763. Doi: 10.1074/jbc.M411325200
7. Petek M, Baebler S, Kuzman D, et al. Revealing fosfomycin primary effect on *Staphylococcus aureus* transcriptome: modulation of cell envelope biosynthesis and phosphoenolpyruvate induced starvation. BMC Microbiol 2010 10:159. <http://dx.doi.org/10.1186/1471-2180-10-159>.
8. Carbone NA, Borsotto M, Cuffini AM, et al. Effect of fosfomycin trometamol on bacterial adhesion in comparison with other chemotherapeutic agents. Eur Urol 1987;13(Suppl 1):S86–S91. Doi: 10.1159/000472869
9. Yokota S, Okabayashi T, Yoto Y, et al. Fosfomycin suppresses RS-virus-in-

- duced *Streptococcus pneumoniae* and *Haemophilus influenzae* adhesion to respiratory epithelial cells via the platelet-activating factor receptor. *FEMS Microbiol Lett* 2010;310(1):84–90. Doi: 10.1111/j.1574-6968.2010.02049.x.
- 10. Matsumoto T, Tateda K, Miyazaki S, et al. Fosfomycin alters lipopolysaccharide induced inflammatory cytokine production in mice. *Antimicrob Agents Chemother* 1999;43(3):697–698.
 - 11. Morikawa K, Watabe H, Araake M, et al. Modulatory effect of antibiotics on cytokine production by human monocytes in vitro. *Antimicrob Agents Chemother* 1996;40(6):1366–1370.
 - 12. Morikawa K, Zhang J, Nonaka M, et al. Modulatory effect of macrolide antibiotics on the Th1- and Th2-type cytokine production. *Int J Antimicrob Agents* 2002;19(1):53–59. Doi: 10.1016/s0924-8579(01)00457-5.
 - 13. Morikawa K, Oseko F, Morikawa S, et al. Immunosuppressive activity of fosfomycin on human T-lymphocyte function in vitro. *Antimicrob Agents Chemother* 1993;37(12):2684–2687. Doi: 10.1128/aac.37.12.2684.
 - 14. Honda J, Okubo Y, Kusaba M, et al. Fosfomycin (FOM: 1 R-2S-epoxy-propylphosphonic acid) suppress the production of IL-8 from monocytes via the suppression of neutrophil function. *Immunopharmacology* 1998 39(2):149–155. Doi: 10.1016/s0162-3109(98)00003-4.
 - 15. European Committee on Antimicrobial Susceptibility Testing. 2020. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0. www.eucast.org/
 - 16. Performance Standards for Antimicrobial Susceptibility Testing. 2020. 30nd informational supplement M100- ED30. Clinical and Laboratory Standards Institute, Wayne, PA.
 - 17. Karlowsky JA, Denisuik AJ, Lagace-Wiens PR, et al. In vitro activity of fosfomycin against *Escherichia coli* isolated from patients with urinary tract infections in Canada as part of The CANWARD surveillance study. *Antimicrob Agents Chemother* 2014; 58(2):1252–1256. Doi: 10.1128/AAC.02399-13
 - 18. Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. *Int. J. Infect. Dis.* 2011;15(11): e732–e739. Doi: 10.1016/j.ijid.2011.07.007.
 - 19. Barry AL, Brown SD. Antibacterial spectrum of fosfomycin trometamol. *J. Antimicrob. Chemother.* 1995;35(1):228–230. Doi: 10.1093/jac/35.1.228.
 - 20. Patel SS, Balfour JA, Bryson HM. Fosfomycin tromethamine. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs* 1997; 53(4):637–656. Doi: 10.2165/00003495-199753040-00007
 - 21. Araj GF, Jaber FA. In vitro activity of fosfomycin and other antimicrobials against uropathogenic *Escherichia coli* and *Klebsiella pneumoniae* at a tertiary care center in Lebanon. *J Med Liban* 2012; 60(3):142–147.
 - 22. Asencio MA, Huertas M, Carranza R, et al. Trend in the susceptibility of the most frequent bacterial pathogens isolated at Hospital General La Mancha

- Centro over 2010-2012 period. Rev Esp Quimioter 2014; 27(4):261–268.
- 23. Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, et al. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)- producing enterobacteria. Int J Clin Pract 2012;66(9):891– 896. Doi: 10.1111/j.1742-1241.2012.02991.x.
 - 24. Cagan Aktas S, Gencer S, Batirel A, et al. Fosfomycin susceptibility of urinary Escherichia coli isolates producing extended-spectrum beta-lactamase according to CLSI and EUCAST recommendations. Mikrobiyol Bul 2014; 48(4):545–555.
 - 25. Champion EA, Miller MB, Popowitch EB, et al. Antimicrobial susceptibility and molecular typing of MRSA in cystic fibrosis. Pediatr Pulmonol 2014; 49(3):230–237. Doi: 10.1002/ppul.22815.
 - 26. Cho YH, Jung SI, Chung HS, et al. Antimicrobial susceptibilities of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in health care-associated urinary tract infection: focus on susceptibility to fosfomycin. Int Urol Nephrol 2015; 47(7):1059–1066. Doi: 10.1007/s11255-015-1018-9.
 - 27. Hsu MS, Liao CH, Liu CY, et al. In vitro susceptibilities of clinical isolates of ertapenem-non-susceptible Enterobacteriaceae to nemonoxacin, tigecycline, fosfomycin and other antimicrobial agents. Int J Antimicrob Agents 2011;37(3):276–278. Doi: 10.1016/j.ijantimicag.2010.12.003.
 - 28. Lai B, Zheng B, Li Y, et al. In vitro susceptibility of Escherichia coli strains isolated from urine samples obtained in mainland China to fosfomycin trometamol and other antibiotics: a 9-year surveillance study (2004–2012). BMC Infect Dis 2014; 14:66. Doi: 10.1186/1471-2334-14-66.
 - 29. Sultan A, Rizvi M, Khan F, et al. Increasing antimicrobial resistance among uropathogens: is fosfomycin the answer? Urol Ann 2015; 7(1):26 –30. Doi: 10.4103/0974-7796.148585.
 - 30. Tuon FF, Rocha JL, Formighieri MS, et al. Fosfomycin susceptibility of isolates with blaKPC-2 from Brazil. J Infect 2013; 67(3):247–249. Doi: 10.1016/j.jinf.2013.04.017.
 - 31. Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of Escherichia coli from community-acquired urinary tract infections in Europe: the ECO-SENS study revisited. Int J Antimicrob Agents 2012; 39(1):45–51. Doi: 10.1016/j.ijantimicag.2011.09.013.
 - 32. Falagas ME, Maraki S, Karageorgopoulos DE, et al. Antimicrobial susceptibility of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Enterobacteriaceae isolates to fosfomycin. Int J Antimicrob Agents 2010; 35(3):240–243. Doi: 10.1016/j.ijantimicag.2009.10.019.
 - 33. Falagas ME, Kastoris AC, Karageorgopoulos DE, et al. Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: A systematic review of microbiological, animal and clinical studies. Int. J. Antimicrob. Agents 2009;34(2):111–120. Doi: 10.1016/j.ijantimicag.2009.03.009.

34. Dinh A, Salomon J, Bru JP, et al. Fosfomycin: Efficacy against infections caused by multidrug resistant bacteria. *Scand J Infect Dis.* 2012;44(3): 182–189. Doi: 10.3109/00365548.2011.616221
35. Falagas ME, Kanellopoulou MD, Karageorgopoulos DE, et al. Antimicrobial susceptibility of multidrug-resistant Gram negative bacteria to fosfomycin. *Eur. J. Clin. Microbiol. Infect. Dis.* 2008, 27(6):439–443. Doi: 10.1007/s10096-007-0456-4.
36. Leite GC, Oliveire MS, Perdiago LV, et al. Antimicrobial combinations against pan-resistant *Acinetobacter baumannii* isolates with different resistance mechanisms. *PLoS One.* 2016; 11(3): e0151270. Doi: 10.1371/journal.pone.0151270
37. Zhang Y, Chen F, Sun E, et al. *In vitro* antibacterial activity of combinations of fosfomycin, minocycline and polymyxin B on pan-drug-resistant *Acinetobacter baumannii*. *Experimental Therapeutic Medic.* 2013;5(6):1737–1739. Doi: 10.3892/etm.2013.1039.
38. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. *Antimicrob Agents Chemother.* 2014;58(9):5598–601. Doi: 10.1128/AAC.02435-13.
39. Falagas ME, Roussos N, Gkekkes ID, et al. Fosfomycin for the treatment of infections caused by Gram positive cocci with advanced antimicrobial drug resistance: a review of microbiological, animal and clinical studies. *Expert Opin Invest Drugs* 2009;18(7):921–944. Doi: 10.1517/13543780902967624.
40. Falagas ME, Kastoris AC, Karageorgopoulos DE, et al. Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: a systematic review of microbiological, animal and clinical studies. *Int J Antimicrob Agents* 2009;34(2):111–120. Doi: 10.1016/j.ijantimicag.2009.03.009.
41. Falagas ME, Kastoris AC, Kapaskelis AM, et al. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010;10(1):43–50. Doi: 10.1016/S1473-3099(09)70325-1.
42. Marchese A, Bozzolasco M, Gualco L, et al. Effect of fosfomycin alone and in combination with N-acetylcysteine on *E. coli* biofilms. *Int J Antimicrob Agents* 2003; 22(Suppl 2):S95–S100. Doi: 10.1016/s0924-8579(03)00232-2.
43. Descourouez JL, Jorgenson MR, Wergin JE, et al. Fosfomycin synergy in vitro with amoxicillin, daptomycin, and linezolid against vancomycin-resistant *Enterococcus faecium* from renal transplant patients with infected urinary stents. *Antimicrob Agents Chemother* 2013;57(3):1518–1520. Doi: 10.1128/AAC.02099-12.
44. Tang HJ, Chen CC, Zhang CC, et al. In vitro efficacy of fosfomycin-based combinations against clinical vancomycin-resistant *Enterococcus* isolates. *Diagn Microbiol Infect Dis* 2013;77(3):254–257. Doi: 10.1016/j.diagnmicrobio.2013.07.012.

45. Pogue JM, Marchaim D, Abreu-Lanfranco O, et al. Fosfomycin activity versus carbapenem resistant Enterobacteriaceae and vancomycin-resistant Enterococcus, Detroit, 2008-10. *J Antibiot (Tokyo)* 2013;66:625– 627. Doi: 10.1038/ja.2013.56.
46. Karageorgopoulos DE, Wang R, Yu XH, et al. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. *J Antimicrob Chemother* 2012;67(2):255–268. Doi: 10.1093/jac/dkr466.
47. McCoy AJ, Sandlin RC, Maurelli AT. In vitro and in vivo functional activity of Chlamydia MurA, a UDP-N-acetylglucosamine enolpyruvyl transferase involved in peptidoglycan synthesis and fosfomycin resistance. *J Bacteriol* 2003;185(4):1218–1228. DOI: 10.1128/jb.185.4.1218-1228.2003.
48. De Smet KA, Kempsell KE, Gallagher A, et al. Alteration of a single amino acid residue reverses fosfomycin resistance of recombinant MurA from *Mycobacterium tuberculosis*. *Microbiology* 1999; 145(Pt 11):3177–3184. Doi: 10.1099/00221287-145-11-3177.
49. Kumar S, Parvathi A, Hernandez RL, et al. Identification of a novel UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) from *Vibrio fischeri* that confers high fosfomycin resistance in *Escherichia coli*. *Arch Microbiol* 2009;191(5):425–429. Doi: 10.1007/s00203-009-0468-9.
50. Borissova M, Gisin J, Mayer C. Blocking peptidoglycan recycling in *Pseudomonas aeruginosa* attenuates intrinsic resistance to fosfomycin. *Microb Drug Resist* 2014;20(3):231–237. Doi: 10.1089/mdr.2014.0036.
51. Tsuruoka T, Miyata A, Yamada Y. Two kinds of mutants defective in multiple carbohydrate utilization isolated from in vitro fosfomycin resistant strains of *Escherichia coli* K-12. *J Antibiot (Tokyo)* 1978; 31(3):192–201. Doi: 10.7164/antibiotics.31.192.
52. Takahata S, Ida T, Hiraishi T, et al. Molecular mechanisms of fosfomycin resistance in clinical isolates of *Escherichia coli*. *Int J Antimicrob Agents* 2010;35(4):333–337. Doi: 10.1016/j.ijantimicag.2009.11.011.
53. Horii T, Kimura T, Sato K, et al. Emergence of fosfomycin-resistant isolates of Shiga-like toxin-producing *Escherichia coli* O26. *Antimicrob Agents Chemother* 1999;43(4):789–793.
54. Nilsson AI, Berg OG, Aspervall O, et al. Biological costs and mechanisms of fosfomycin resistance in *Escherichia coli*. *Antimicrob Agents Chemother* 2003; 47(9):2850–2858. Doi: 10.1128/aac.47.9.2850-2858.2003.
55. Venkateswaran PS, Wu HC. Isolation and characterization of a phosphonomycin-resistant mutant of *Escherichia coli* K-12. *J Bacteriol* 1972;110(3):935–944.
56. Arca P, Reguera G, Hardisson C. Plasmid-encoded fosfomycin resistance in bacteria isolated from the urinary tract in a multicentre survey. *J Antimicrob Chemother* 1997;40(3):393–399. Doi:10.1093/jac/40.3.393.
57. Arca P, Hardisson C, Suarez JE. Purification of a glutathione S-transferase that mediates fosfomycin resistance in bacteria. *Antimicrob Agents Che*

- mother 1990; 34(5):844–848. Doi: 10.1128/aac.34.5.844
58. Arca P, Rico M, Brana AF, et al. Formation of an adduct between fosfomycin and glutathione: a new mechanism of antibiotic resistance in bacteria. *Antimicrob Agents Chemother* 1998; 32(10):1552–1556. Doi: 10.1128/aac.32.10.1552.
59. Bernat BA, Laughlin LT, Armstrong RN. Fosfomycin resistance protein (FosA) is a manganese metalloglutathione transferase related to glyoxalase I and the extradiol dioxygenases. *Biochemistry* 1997; 36(11):3050–3055. Doi: 10.1021/bi963172a.
60. Ma Y, Xu X, Guo Q, et al. Characterization of fosA5, a new plasmid-mediated fosfomycin resistance gene in *Escherichia coli*. *Lett Appl Microbiol* 2015; 60:259–264.
61. Wachino J, Yamane K, Suzuki S, et al. Prevalence of fosfomycin resistance among CTX-M-producing *Escherichia coli* clinical isolates in Japan and identification of novel plasmid mediated fosfomycin-modifying enzymes. *Antimicrob Agents Chemother* 2010; 54(7):3061–3064. Doi: 10.1128/AAC.01834-09.
62. Xu H, Miao V, Kwong W, et al. Identification of a novel fosfomycin resistance gene (fosA2) in *Enterobacter cloacae* from the Salmon River, Canada. *Lett Appl Microbiol* 2011; 52(4):427–429. Doi: 10.1111/j.1472-765X.2011.03016.x.
63. Zhao JY, Zhu YQ, Li YN, et al. Coexistence of SFO-1 and NDM-1 beta-lactamase genes and fosfomycin resistance gene fosA3 in an *Escherichia coli* clinical isolate. *FEMS Microbiol Lett* 2015; 362(1):1–7. Doi: 10.1093/femsle/fnu018.
64. Qu TT, Shi KR, Ji JS, et al. Fosfomycin resistance among vancomycin-resistant enterococci owing to transfer of a plasmid harbouring the fosB gene. *Int J Antimicrob Agents* 2014;43(4):361–365. Doi: 10.1016/j.ijantimicag.2013.11.003.
65. Xu X, Chen C, Lin D, et al. The fosfomycin resistance gene fosB3 is located on a transferable, extrachromosomal circular intermediate in clinical *Enterococcus faecium* isolates. *PLoS One* 2013; 8:e78106. Doi: 10.1371/journal.pone.0078106.
66. Cao M, Bernat BA, Wang Z, et al. FosB, a cysteine-dependent fosfomycin resistance protein under the control of sigma (W), an extracytoplasmic-function sigma factor in *Bacillus subtilis*. *J Bacteriol* 2001;183(7):2380–2383. Doi: 10.1128/JB.183.7.2380-2383.2001.
67. Etienne J, Gerbaud G, Fleurette J, et al. Characterization of staphylococcal plasmids hybridizing with the fosfomycin resistance gene fosB. *FEMS Microbiol Lett* 1991; 68(1):119–122. Doi: 10.1016/0378-1097(91)90406-z.
68. Zilhao R, Courvalin P. Nucleotide sequence of the fosB gene conferring fosfomycin resistance in *Staphylococcus epidermidis*. *FEMS Microbiol Lett* 1990; 56(3):267–272. Doi: 10.1016/s0378-1097(05)80052-7
69. Fillgrove KL, Pakhomova S, Schaab MR, et al. Structure and mechanism of

- the genomically encoded fosfomycin resistance protein, FosX, from *Listeria monocytogenes*. *Biochemistry* 2007; 46(27):8110–8120. Doi: 10.1021/bi700625p.
- 70. Garcia P, Arca P, Evaristo Suarez J. Product of fosC, a gene from *Pseudomonas syringae*, mediates fosfomycin resistance by using ATP as cosubstrate. *Antimicrob Agents Chemother* 1995; 39(7):1569–1573. Doi: 10.1128/aac.39.7.1569.
 - 71. Duez JM, Mousson C, Siebor E, et al. Fosfomycin and its application in the treatment of multidrug-resistant Enterobacteriaceae infections. *Clin Med Rev Ther* 2011; 3:123–142. Doi: 10.4137/CMRTS5102.
 - 72. Engel H, Gutierrez-Fernandez J, Fluckiger C, et al. Heteroresistance to fosfomycin is predominant in *Streptococcus pneumoniae* and depends on the murA1 gene. *Antimicrob Agents Chemother* 2013; 57(6):2801–2808. Doi: 10.1128/AAC.00223-13.
 - 73. Walsh CC, McIntosh MP, Peleg AY, et al. In vitro pharmacodynamics of fosfomycin against clinical isolates of *Pseudomonas aeruginosa*. *J Antimicrob Chemother* 2015; 70(11):3042–3050. Doi: 10.1093/jac/dkv221.
 - 74. Bergan T. Pharmacokinetics of fosfomycin. *Rev Contemp Pharmacother* 1995;6:55–62.
 - 75. Segre G, Bianchi E, Cataldi A, et al. Pharmacokinetic profile of fosfomycin trometamol (Monuril). *Eur Urol* 1987;13(Suppl 1):56–63.
 - 76. Sicilia T, Estévez E, Rodríguez A. Fosfomycin penetration into the cerebrospinal fluid of patients with bacterial meningitis. *Cancer Chemotherapy* 1981;27(6):405–413. Doi: 10.1159/000238009.
 - 77. Borgia M, Longo A, Lodola E. Relative bioavailability of fosfomycin and of trometamol after administration of single dose by oral route of fosfomycin trometamol in fasting conditions and after a meal. *Int J Clin Pharmacol Ther* 1989; 27(8):411–417.
 - 78. Soraci AL, Perez DS, Martinez G, et al. Disodium-fosfomycin pharmacokinetics and bioavailability in post weaning piglets. *Res Vet Sci* 2011; 90(3):498–502. Doi: 10.1016/j.rvsc.2010.07.011
 - 79. Sumano LH, Ocampo CL, Gutierrez OL. Intravenous and intramuscular pharmacokinetics of a single-daily dose of disodiumfosfomycin in cattle, administered for 3 days. *J Vet Pharmacol Ther* 2007; 30(1): 49–54. Doi: 10.1111/j.1365-2885.2007.00812.x
 - 80. Roussos N, Karageorgopoulos DE, Samonis G, et al. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. *Int J Antimicrob Agents* 2009; 34(6):506–515. Doi: 10.1016/j.ijantimicag.2009.08.013.
 - 81. Bergan T, Thorsteinsson SB, Albini E. Pharmacokinetic profile of fosfomycin trometamol. *Cancer Chemotherapy* 1993; 39(5):297–301. Doi: 10.1159/000239140
 - 82. Pfausler B, Spiss H, Dittrich P, Zeitlinger M, Schmutzhard E, Joukhadar C. Concentrations of fosfomycin in the cerebrospinal fluid of neurointensive care patients with ventriculostomy-occluded ventriculitis. *J. Antimicrob.*

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- Chemother. 2004;53(5):848–852. Doi: 10.1093/jac/dkh158.
83. Frossard M, Joukhadar C, Erovic BM, et al. Distribution and antimicrobial activity of fosfomycin in the interstitial fluid of human soft tissues. *Antimicrob. Agents Chemother.* 2000;44(10): 2728–2732. Doi: 10.1128/aac.44.10.2728-2732.2000.
84. Matzi V, Lindenmann JP, Porubsky C, et al. Extracellular concentrations of fosfomycin in lung tissue of septic patients. *J. Antimicrob. Chemother.* 2010;65(5):995–998. Doi: 10.1093/jac/dkq070.
85. Falagas ME, Vouloumanou EK, Samonis G, et al. Fosfomycin. *Clin Microbiol Rev.* 2016;29(2):321–347. Doi: 10.1128/CMR.00068-15.
86. Mayama T, Yokota M, Shimatani I, et al. Analysis of oral fosfomycin calcium (Fosmicin) side-effects after marketing. *Int J Clin Pharmacol Ther Toxicol* 1993;31(2):77–82.
87. Falagas ME, Giannopoulou KP, Kokolakis GN, et al. Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis* 2008;46(7):1069-1077. Doi: 10.1086/527442.