

Fosfomycin

A phosphonic acid bactericidal MurA inhibitor that blocks the very first step of peptidoglycan synthesis - clinically defined by single-dose oral therapy for uncomplicated cystitis and retained activity against many drug-resistant uropathogens.

Online guide: <https://www.medguideglobal.com/pharmacology/antibiotics/fosfomycin>

Content updated: 2026-08-17

Quick revision

One Liner: Fosfomycin covalently inactivates MurA, the enolpyruvyl transferase that commits UDP-NAG to peptidoglycan synthesis - the earliest cell-wall step any antibiotic hits - and rides bacterial sugar transporters into the cell, which is exactly where resistance arises.

1. Mechanism: inhibits MurA (UDP-N-acetylglucosamine enolpyruvyl transferase), blocking the first committed step of peptidoglycan synthesis, upstream of every -lactam and glycopeptide target. [1]
2. Bactericidal, and structurally unrelated to any other antibiotic class - a phosphonic acid (epoxide) natural product of *Streptomyces*, so there is no cross-resistance with -lactams. [2][1]
3. Cell entry is active, via the GlpT (glycerophosphate) and UhpT (glucose-6-phosphate) transporters; loss or downregulation of these transporters is the classic resistance mechanism. [1]
4. Clinical niche: FDA-approved as single-dose oral therapy for uncomplicated urinary tract infection in women, given as a sachet dissolved in water. [3][4]
5. Covers *Escherichia coli* - including many ESBL producers and other drug-resistant strains - and *Enterococcus faecalis*, the two labelled organisms for uncomplicated cystitis. [4][3]
6. A single oral dose maintains therapeutic urinary concentrations for 2 to 4 days, comparable to a 7- to 10-day course of other agents. [3]
7. Generally well tolerated: diarrhoea, nausea and headache are the common complaints; clinically apparent liver injury is rare (LiverTox likelihood score D). [4][2]
8. Metoclopramide lowers fosfomycin serum concentrations and urinary excretion by speeding gastrointestinal transit - the one interaction worth memorising. [4]

Overview

1. Fosfomycin is a phosphonic acid antibiotic, a natural product of *Streptomyces* discovered in 1969 and approved in the United States in 1997, that occupies a class of one: no other marketed antibiotic shares its structure, its target or its uptake route. It is broad-spectrum and bactericidal, and in most of the world its defining presentation is a single-dose oral sachet for uncomplicated urinary tract infection. [2][1]
2. Its mechanism is the earliest attack on the bacterial cell wall in all of pharmacology. Fosfomycin covalently inactivates MurA, the enolpyruvyl transferase that commits UDP-N-acetylglucosamine to the peptidoglycan pathway - the first step in building the NAM precursor. Because -lactams and glycopeptides act far downstream, ESBL producers and many otherwise multidrug-resistant organisms remain susceptible, which is why an old drug has become newly important. [1][3]
3. The clinical story is one of deliberate restraint. The oral product is first-line for uncomplicated cystitis in women, covering *E. coli* - including resistant strains - and *Enterococcus faecalis*, and it is generally well tolerated, with diarrhoea, nausea and headache the common complaints. It is not for pyelonephritis, where tissue concentrations are inadequate; and in some countries an intravenous form is reserved, usually in combination, for multidrug-resistant infections. [4][3][2][1]

Classification and drug examples

Intro: A single-agent class: fosfomycin is the only phosphonic acid antibiotic in clinical use, so classification is by salt and route rather than by chemical subclass.

1. Name: Oral fosfomycin (tromethamine salt)

1. Note: The tromethamine (trometamol) salt improves oral bioavailability and is supplied as a sachet of granules dissolved in water - the single-dose cystitis product.

Name: Fosfomycin tromethamine

1. Monurol

2. fosfomycin trometamol

Route: Oral (sachet)

Note: Single-dose therapy for uncomplicated urinary tract infection in women, caused by susceptible E. coli or Enterococcus faecalis. [4][3] [4][2]

2. Name: Intravenous fosfomycin (disodium salt)

2. Note: Available in some countries, not the United States, and used - usually in combination with another agent - against multidrug-resistant gram-negative and gram-positive infections.

Name: Fosfomycin disodium

Route: IV

Note: Carries a substantial sodium load; specialist, combination use for MDR infection where marketed. [1] [1][2]

Mechanism of action

Summary: Fosfomycin enters the bacterium through the GlpT and UhpT sugar-phosphate transporters and covalently inactivates MurA, the enolpyruvyl transferase catalysing the first committed step of peptidoglycan synthesis, halting cell-wall precursor production before any -lactam target is even reached.

Target: MurA (UDP-N-acetylglucosamine enolpyruvyl transferase), the first committed enzyme of peptidoglycan synthesis

Cidal Static: bactericidal

Kill Kinetics: time-dependent in most models; sustained urinary concentrations after a single oral dose do the clinical work

1. Step: 1

1. Title: Active transport into the cell

1. Detail: Fosfomycin resembles glycerophosphate and glucose-6-phosphate closely enough to be carried in by the GlpT and UhpT transporters - it does not simply diffuse across the membrane. [1]

2. Step: 2

2. Title: Recognition by MurA

2. Detail: Inside the cytoplasm the drug binds the active site of MurA, the enzyme that transfers enolpyruvate from phosphoenolpyruvate onto UDP-N-acetylglucosamine. [1]

3. Step: 3

3. Title: Covalent inactivation

3. Detail: Fosfomycin's epoxide ring opens to form a covalent adduct with the active-site cysteine of MurA - a dead-end inhibition that requires UDP-NAG binding and permanently disables the enzyme molecule. [1]

4. Step: 4

4. Title: Peptidoglycan synthesis stops at step one

4. Detail: With MurA blocked, enolpyruvyl-UDP-NAG - the precursor on the path from NAG to NAM - is never made, so no muramyl building blocks reach the downstream pathway that -lactams and glycopeptides act on. [1]

5. Step: 5

5. Title: The wall fails and the organism dies

5. Detail: Loss of peptidoglycan synthesis is lethal to a growing bacterium; the effect is bactericidal, and because no other antibiotic shares this target there is no cross-resistance with other cell-wall agents. [1][2]

Spectrum of activity

Intro: Broad in vitro activity across gram-negative and gram-positive organisms; the labelled clinical spectrum is narrower, defined by the urinary niche.

Subclass Id: class-wide

1. Enterococcus faecalis
2. Activity reported against other gram-positive organisms, including some vancomycin-resistant strains
 1. Escherichia coli, including many ESBL-producing and otherwise drug-resistant strains
 2. Other Enterobacterales with variable susceptibility
1. Upper urinary tract and systemic infection by the oral route - tissue levels are insufficient for pyelonephritis
2. Intrinsically less susceptible organisms encountered outside the labelled cystitis indication [4][3][1]

Major clinical uses

1. Drug: Fosfomycin tromethamine
 1. Organism: Escherichia coli, including many drug-resistant strains
 1. Indication: Uncomplicated urinary tract infection (acute cystitis) in women
 1. Line: first-line
 1. Note: Single-dose oral therapy; one of the recommended first-line agents alongside nitrofurantoin and trimethoprim-sulfamethoxazole. [3][4]
 2. Drug: Fosfomycin tromethamine
 2. Organism: Enterococcus faecalis
 2. Indication: Uncomplicated urinary tract infection where E. faecalis is the susceptible pathogen
 2. Line: first-line
 2. Note: The second labelled organism for the single-dose oral indication. [4]
 3. Drug: Fosfomycin tromethamine
 3. Organism: ESBL-producing and multidrug-resistant uropathogens
 3. Indication: Lower urinary tract infection where resistance rules out other oral first-line agents
 3. Line: targeted
 3. Note: Retained activity against many resistant organisms is the main reason for the drug's modern resurgence; use should follow susceptibility results. [3][1]
 4. Drug: Fosfomycin disodium (IV)
 4. Organism: Multidrug-resistant gram-negative and gram-positive organisms
 4. Indication: Serious MDR infection, in countries where the IV form is marketed
 4. Line: reserve
 4. Note: Specialist use, almost always in combination with another active agent to protect against emergence of resistance on therapy. [1][2]

Pharmacokinetics

Drug: Fosfomycin tromethamine

Route: Oral (sachet of granules dissolved in water)

Absorption: Absorbed after oral dosing as the tromethamine salt; absorption falls when gastrointestinal transit is accelerated, as with metoclopramide

Csf Penetration: Not relevant to the labelled indication

Metabolism: Minimal hepatic metabolism

Elimination: Renal, excreted unchanged in urine - which is precisely what makes the urinary niche work

Half Life: Therapeutic urinary concentrations persist 2 to 4 days after a single dose

Dose Adjust: See prescribing reference; not appropriate for pyelonephritis, where tissue levels are insufficient [4][3][2]

1. The single-dose characteristic is pharmacokinetic, not a marketing convenience: high, sustained urinary drug concentrations after one oral dose give clinical cure rates comparable to a 7- to 10-day course of other first-line cystitis agents. [3]

2. Fosfomycin undergoes minimal hepatic metabolism, mostly glucuronidation, which fits its low rate of liver-related adverse events. [2]

3. This page gives no dose regimens by design. Doses depend on indication, formulation, renal function and local licensing, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Gastrointestinal upset

1. Detail: Diarrhoea and nausea are the most frequent complaints after the single oral dose; the drug is otherwise generally well tolerated. [4][2]

2. Effect: Headache

2. Detail: Among the commonly reported adverse events in trials of the single-dose product, alongside vaginitis and dizziness. [4]

1. Effect: Clinically apparent liver injury

1. Detail: Rare. Transient aminotransferase elevations occur in 1 to 2% of patients after a single dose - rates similar to comparator antibiotics - and reported clinical injury has been mild and self-limited, with no fatal acute liver failure documented (LiverTox likelihood score D).

1. Action: No routine monitoring is needed for single-dose use; investigate jaundice or persistent symptoms as for any suspected drug-induced liver injury. [2]

2. Effect: Hypersensitivity reactions

2. Detail: Reported with fosfomycin as with other antibiotics; prior hypersensitivity to the drug contraindicates re-exposure.

2. Action: Stop the drug and manage as for drug allergy. [4]

Drug: Fosfomycin disodium (IV)

Effect: Carries a substantial sodium load per dose, relevant in heart failure and renal impairment where the IV form is used. [1]

Contraindications, precautions and interactions

Known hypersensitivity to fosfomycin. [4]

1. Known or suspected pyelonephritis or perinephric abscess - the single-dose oral product is not indicated, because renal tissue levels are insufficient. [4][3]

2. Persistent or recurrent symptoms after single-dose therapy call for urine culture and a different agent, not repeated dosing of the sachet. [4]

1. With: Metoclopramide and other drugs that increase gastrointestinal motility

1. Effect: Lower fosfomycin serum concentrations and urinary excretion, risking treatment failure of the single oral dose. [4]

2. With: Cimetidine

2. Effect: No effect on fosfomycin pharmacokinetics - a documented negative that examiners pair with the metoclopramide interaction. [4]

Resistance mechanisms

1. Mechanism: Loss of the uptake transporters

1. Detail: Because fosfomycin depends on GlpT and UhpT for entry, mutations that inactivate or downregulate these transporters (or their regulators) deny the drug access to MurA - the most common resistance route, though such mutants often carry a fitness cost in the urinary tract.

GlpT or UhpT loss in *E. coli*

1. Countermeasure: Susceptibility testing before use outside the empiric cystitis niche; combination therapy in serious IV use. [1]

2. Mechanism: Target modification

2. Detail: Mutation of the MurA active-site cysteine prevents formation of the covalent fosfomycin adduct; some species carry intrinsically resistant MurA variants.

MurA active-site mutants

2. Countermeasure: Choose an agent from a different mechanistic class. [1]

3. Mechanism: Fosfomycin-modifying enzymes

3. Detail: Enzymes such as FosA conjugate glutathione onto the epoxide ring, inactivating the drug; these can be chromosomal or plasmid-borne, and plasmid spread is the stewardship concern.

FosA in gram-negative organisms

3. Countermeasure: Surveillance and susceptibility-directed use. [1]

Stewardship Note: Fosfomycin's value in the ESBL era rests on its unique target and lack of cross-resistance. Keeping it useful means keeping it in its lane: single-dose therapy for uncomplicated cystitis, and susceptibility-directed, usually combination, use anywhere more serious.

Comparison tables

Title: Fosfomycin against the other first-line cystitis agents

Caption: How the single-dose sachet sits alongside the other first-line oral options for uncomplicated urinary tract infection. Local resistance data and a prescribing reference govern actual therapy.

1. Key: feature

1. Label: Feature

1. Is Row Header: true

2. Key: fosfomycin

2. Label: Fosfomycin

3. Key: nitrofurantoin

3. Label: Nitrofurantoin

4. Key: tmp_smx

4. Label: Trimethoprim-sulfamethoxazole

1. Feature: Mechanistic target

1. Fosfomycin: MurA - first step of peptidoglycan synthesis

1. Nitrofurantoin: Reduced intermediates damage multiple bacterial macromolecules

1. Tmp Smx: Sequential folate synthesis blockade [1][3]

2. Feature: Course for uncomplicated cystitis

2. Fosfomycin: Single oral dose

2. Nitrofurantoin: Multi-day course

2. Tmp Smx: Short multi-day course [3]

3. Feature: Activity against ESBL *E. coli*

3. Fosfomycin: Largely retained

3. Nitrofurantoin: Often retained

- 3. Tmp Smx: Frequently lost with co-carried resistance [3][1]
- 4. Feature: Use in pyelonephritis
- 4. Fosfomycin: No - insufficient tissue levels
- 4. Nitrofurantoin: No - insufficient tissue levels
- 4. Tmp Smx: Yes, if the isolate is susceptible [3]

High-yield exam pearls

- 1. Pearl: Fosfomycin hits the cell wall earlier than anything else.
 - 1. Why: MurA catalyses the first committed cytoplasmic step of peptidoglycan synthesis - transfer of enolpyruvate from PEP onto UDP-N-acetylglucosamine, on the path to the NAM precursor. -lactams and glycopeptides act far downstream, at cross-linking and polymerisation, which is why fosfomycin shares no target and no cross-resistance with them. [1]
- 2. Pearl: The drug is smuggled in on sugar-phosphate transporters.
 - 2. Why: Fosfomycin mimics glycerophosphate and glucose-6-phosphate closely enough to enter via GlpT and UhpT. That dependence is a vulnerability: mutants that lose the transporter lose susceptibility, which is the most common resistance route. [1]
- 3. Pearl: Its defining feature is single-dose oral therapy, approved for uncomplicated cystitis in women when prescribed by a clinician.
 - 3. Why: Therapeutic urinary concentrations persist for 2 to 4 days after one dose, which is why trials report cure rates comparable to a 7- to 10-day course of other first-line agents. Suitability, and whether the infection is genuinely uncomplicated, are clinical judgements. [3]
- 4. Pearl: ESBL production does not defeat fosfomycin.
 - 4. Why: Extended-spectrum -lactamases hydrolyse -lactams; fosfomycin is not a -lactam and MurA is not a -lactamase substrate, so activity against many ESBL-producing E. coli is retained - the reason fosfomycin resurfaced in the multidrug-resistance era. [1][3]
- 5. Pearl: Metoclopramide is the interaction examiners ask about.
 - 5. Why: By increasing gastrointestinal motility it lowers fosfomycin serum concentrations and urinary excretion; other promotility drugs may do the same. Cimetidine, by contrast, has no effect on fosfomycin pharmacokinetics. [4]
- 6. Pearl: An IV form exists for MDR infections outside the sachet niche.
 - 6. Why: Intravenous fosfomycin (disodium salt) is available in some countries and used, usually in combination, against multidrug-resistant gram-negative and gram-positive infections - a different role from the single-dose oral product. [1][2]

Common exam traps

- 1. Trap: "Fosfomycin is a -lactam because it inhibits cell wall synthesis."
 - 1. Correction: It is a phosphonic acid derivative, structurally unrelated to -lactams, and acts on MurA in the cytoplasm - the earliest peptidoglycan step - not on penicillin-binding proteins. There is no cross-resistance with -lactams. [1][2]
- 2. Trap: "A drug good for cystitis must be good for pyelonephritis."
 - 2. Correction: Single-dose oral fosfomycin is for uncomplicated lower urinary tract infection. It is not appropriate for known or suspected pyelonephritis, where tissue levels are insufficient. [3][4]
- 3. Trap: "Fosfomycin resistance works like -lactam resistance."
 - 3. Correction: The characteristic route is loss of the GlpT or UhpT uptake transporters (with target modification and fosfomycin-modifying enzymes such as FosA also described), not -lactamase production - a direct consequence of its unique entry mechanism and target. [1]
- 4. Trap: "Single-dose means the symptoms resolve the same day."
 - 4. Correction: Urinary concentrations remain therapeutic for 2 to 4 days after the dose, and clinical response is judged over that window; a persistent infection needs reassessment, not automatic redosing. [3]

Self-test questions

1. Question: Fosfomycin exerts its bactericidal effect by covalently inactivating which enzyme?

1. Penicillin-binding protein 2a
2. D-alanyl-D-alanine ligase
3. The transglycosylase that polymerises glycan chains
4. MurA, the UDP-N-acetylglucosamine enolpyruvyl transferase

1. Explanation: The drug's epoxide ring opens onto an active-site cysteine and forms a dead-end adduct, permanently disabling the enzyme that transfers enolpyruvate from phosphoenolpyruvate onto UDP-N-acetylglucosamine. That reaction commits the sugar to the peptidoglycan route and is the earliest wall-building step any antibiotic attacks, far upstream of where beta-lactams and glycopeptides work. [1]

2. Question: How does fosfomycin gain access to its cytoplasmic target?

1. By simple passive diffusion across the cytoplasmic membrane
2. By carriage on the GlpT and UhpT transporters, whose natural substrates it mimics
3. By reversal of a multidrug efflux pump
4. By binding lipoteichoic acid and translocating with wall turnover

2. Explanation: The molecule resembles glycerophosphate and glucose-6-phosphate closely enough to be picked up by the carriers meant for those sugars, so entry is active rather than incidental. Relying on somebody else's transport system is a liability, and it is precisely why the commonest form of resistance is a mutant that stops making the carrier. [1]

3. Question: Why does fosfomycin retain activity against many ESBL-producing *Escherichia coli*?

1. Phosphonic acids act as direct inhibitors of extended-spectrum beta-lactamases
2. ESBL producers lose the GlpT transporter, which paradoxically increases fosfomycin uptake
3. It carries no beta-lactam ring, and MurA is not something a beta-lactamase can act on
4. The single-dose regimen produces concentrations high enough to saturate any beta-lactamase

3. Explanation: Those enzymes exist to hydrolyse a particular chemical ring, and this compound simply does not have one. Because the target sits at the start of peptidoglycan synthesis rather than among the penicillin-binding proteins, an organism well defended against penicillins and cephalosporins is no better protected here - the reason a drug from the 1960s became newly important in the multidrug-resistance era. [1][3]

4. Question: The single-dose oral sachet of fosfomycin is indicated for which of the following?

1. Uncomplicated lower urinary tract infection in women
2. Known or suspected pyelonephritis
3. Perinephric abscess
4. Systemic gram-negative infection by the oral route

4. Explanation: The labelled role is acute uncomplicated cystitis caused by susceptible *Escherichia coli* or *Enterococcus faecalis*, where the pathogen sits in bladder urine and the drug is excreted unchanged into exactly that compartment. Concentrations in renal tissue are not adequate, so infection that has climbed above the bladder lies outside what this product can do, and persistent symptoms call for culture and a different agent rather than a repeat sachet. [3][4]

5. Question: What is the pharmacokinetic basis for treating uncomplicated cystitis with a single fosfomycin dose?

1. Extensive hepatic metabolism to a long-lived active metabolite
2. Irreversible plasma protein binding that slowly releases free drug
3. Storage within renal tissue with gradual release into the collecting system
4. Excretion of unchanged drug into urine, where concentrations stay therapeutic for two to four days
5. Explanation: Very little of the compound is metabolised; it leaves the body intact by the renal route and remains at active levels in urine across several days. That sustained bladder exposure is what allows one sachet to match the cure rates reported for a seven- to ten-day course of another first-line agent, so the regimen is a consequence of the

pharmacokinetics rather than a marketing convenience. [3][2]

6. Question: Which is the most common route to fosfomycin resistance?

1. Production of extended-spectrum beta-lactamases
2. Mutational loss or downregulation of the GlpT or UhpT uptake transporters
3. Ribosomal protection proteins that displace the drug from its binding site
4. Alteration of penicillin-binding protein affinity

6. Explanation: Shutting the door is easier than changing the lock, so mutants that no longer express the uptake carriers dominate, although such isolates often pay a fitness penalty in the urinary tract. Mutation of the MurA active-site cysteine, which prevents the covalent adduct forming, and glutathione-conjugating enzymes of the FosA family are the other described routes; plasmid spread of the latter is the stewardship worry. [1]

7. Question: Which statement about fosfomycin drug interactions is correct?

1. Cimetidine markedly increases fosfomycin urinary concentrations
2. Metoclopramide raises fosfomycin serum concentrations by delaying gastric emptying
3. Metoclopramide lowers fosfomycin serum concentrations and urinary excretion, while cimetidine leaves its pharmacokinetics unchanged
4. Fosfomycin is a potent CYP3A4 inhibitor and raises concentrations of co-administered statins

7. Explanation: Hurrying material through the gut leaves less opportunity for absorption, and for an agent whose entire strategy rests on one well-absorbed dose that shortfall can mean failure; other promotility drugs may behave the same way. The histamine H2 blocker is the documented negative examiners like to pair with it, having no measurable effect on the drug's handling. [4]

Frequently asked questions

1. Question: Why does fosfomycin still work against ESBL-producing *E. coli*?

1. Answer: ESBLs are β -lactamases - enzymes that destroy β -lactam antibiotics. Fosfomycin is a phosphonic acid with no β -lactam ring, and its target, MurA, sits at the very start of peptidoglycan synthesis, far upstream of the penicillin-binding proteins. Nothing an ESBL does touches it. [1][3]

2. Question: How can a single dose treat an infection?

2. Answer: Fosfomycin is excreted unchanged into the urine, where concentrations stay therapeutic for 2 to 4 days after one oral dose. For an infection confined to bladder urine, that sustained exposure is comparable to a 7- to 10-day course of other agents. [3][2]

3. Question: Why is fosfomycin not used for pyelonephritis?

3. Answer: Because the drug concentrates in urine, not renal tissue. In known or suspected pyelonephritis, tissue levels from the single-dose oral product are insufficient, so a different agent is required. [3][4]

4. Question: How do bacteria become resistant to fosfomycin?

4. Answer: Most commonly by losing the GlpT or UhpT transporters the drug uses to enter the cell. MurA target mutations and fosfomycin-inactivating enzymes such as FosA are also described. Because the target is unique, resistance to other antibiotic classes neither confers nor implies fosfomycin resistance. [1]

5. Question: Why should metoclopramide be avoided around a fosfomycin dose?

5. Answer: Metoclopramide speeds gastrointestinal transit, which lowers fosfomycin serum concentrations and urinary excretion - and for a drug whose entire strategy is one well-absorbed dose, reduced absorption can mean treatment failure. Other promotility drugs may do the same; cimetidine, by contrast, has no effect. [4]

References

[1] Silver LL. Fosfomycin: Mechanism and Resistance (Cold Spring Harbor Perspectives in Medicine). Cold Spring Harbor Laboratory Press / PubMed 2017. <https://pubmed.ncbi.nlm.nih.gov/28062557/>

[2] Fosfomycin (LiverTox). LiverTox, NIDDK / NCBI Bookshelf 2018. <https://www.ncbi.nlm.nih.gov/books/NBK547912/>

[3] Uncomplicated Urinary Tract Infections (StatPearls). StatPearls Publishing / NCBI Bookshelf 2025.

<https://www.ncbi.nlm.nih.gov/books/NBK470195/>

[4] Monurol (fosfomycin tromethamine) sachet - FDA prescribing information. U.S. Food and Drug Administration 2008.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050717s005lbl.pdf

For education only. This guide does not replace professional medical advice. Do not use it to choose or change treatment.