SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fomicyt 2g
Fomicyt 4g
Fomicyt 8g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution for infusion contains 40 mg fosfomycin.

Each bottle with 2.69 g of powder contains 2.64 g disodium fosfomycin, corresponding to 2 g fosfomycin and 0.64 g sodium, for solution in 50 ml of solvent.

Each bottle with 5.38 g of powder contains 5.28 g disodium fosfomycin, corresponding to 4 g fosfomycin and 1.28 g sodium, for solution in 100 ml of solvent.

Each bottle with 10.76 g of powder contains 10.56 g disodium fosfomycin, corresponding to 8 g fosfomycin and 2.56 g sodium, for solution in 200 ml of solvent.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
White to cream-coloured powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Fomicyt is indicated in all age groups for the treatment of the following infections when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment (see sections 4.2, 4.4 and 5.1):

- complicated urinary tract infections
- infective endocarditis
- bone and joint infections
- hospital-acquired pneumonia, including ventilator-associated pneumonia
- complicated skin and soft tissue infection
- bacterial meningitis
- complicated intra-abdominal infections
- bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The daily dose of fosfomycin is determined based on the indication, severity and site of the infection, susceptibility of the pathogen(s) to fosfomycin and the renal function. In children, it is also determined by age and body weight.

Adults and adolescents (≥ 12 years of age) (≥ 40 kg):

The general dosage guidelines for adults and adolescents with estimated creatinine clearance > 80 ml/min are as follows:

Table 1 – dosing in adults and adolescents with CrCl >80 ml/min

Indication	**Daily dose**
Complicated urinary tract infection	12–24 g [a] in 2–3 divided doses
Infective endocarditis	12–24 g [a] in 2–3 divided doses
Bone and joint infections	12–24 g [a] in 2–3 divided doses
Hospital-acquired pneumonia, including ventilator-associated pneumonia	12–24 g [a] in 2–3 divided doses
Complicated skin and soft tissue infections	12–24 g [a] in 2–3 divided doses
Bacterial meningitis	16–24 g [a] in 3–4 divided doses
Complicated intra-abdominal infections	12–24 g [a] in 2–3 divided doses
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above	12–24 g [a] in 2–3 divided doses

Individual doses must not exceed 8 g.
[a] The high-dose regimen in 3 divided doses should be used in severe infections expected or known to be caused by less susceptible bacteria.
There are limited safety data in particular for doses in excess of 16 g/day. Special caution is advised when such doses are prescribed.

Duration of treatment

Treatment duration should take into account the type of infection, the severity of the infection as well as the patient's clinical response.

Elderly patients

The recommended doses for adults should be used in elderly patients. Caution is advised when considering the use of doses at the higher end of the recommended range (see also recommendations on dosage for patients with impaired renal function).

Renal impairment

No dose adjustment is recommended in patients within estimated creatinine clearance between 40–80 ml/min. However, caution should be exercised in these cases, particularly if doses at the higher end of the recommended range are considered

In patients with impaired renal function the dose of fosfomycin must be adjusted to the degree of renal impairment.

Dose titration should be based on creatinine clearance values.

Table 2 shows the recommended dose adjustments for patients with a CrCL less than 40 mL/min:

Table 2 – Dose adjustments for patients with a CrCL less than 40 mL/min

$CL_{CR\ patient}$	**$CL_{CR\ patient}/CL_{CR\ normal}$**	**Daily dosage recommended[a]**

40 mL/min	0.333	70% (in 2-3 divided doses)
30 mL/min	0.250	60% (in 2-3 divided doses)
20 mL/min	0.167	40% (in 2-3 divided doses)
10 mL/min	0.083	20% (in 1-2 divided doses)

[a] The dose is expressed as a proportion of the dose that would have been considered appropriate if the patient's renal function were normal as calculated according to Cockgroft-Gault formula.

The first dose (loading dose) should be increased by 100%, but must not exceed 8 g.

Patients undergoing renal replacement therapy

Patients undergoing chronic intermittent dialysis (every 48 hours) should receive 2 g of fosfomycin at the end of each dialysis session.

During continuous veno-venous hemofiltration (post-dilution CVVHF), fosfomycin is effectively eliminated. Patients undergoing post-dilution CVVHF will not require any dose adjustment (see section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment.

Paediatric population

Dose recommendations are based on very limited data.

Neonates, infants and children < 12 years of age (< 40 kg)

The dosage of fosfomycin in children should be based on age and body weight (BW):

Table 3 – Dosing in children and neonates

Age/weight	**Daily dose**
Premature neonates (age [a] <40 weeks)	100 mg/kg BW in 2 divided doses
Neonates (age [a] 40-44 weeks)	200 mg/kg BW in 3 divided doses
Infants 1-12 months (up to 10 kg BW)	200-300 [b] mg/kg BW in 3 divided doses
Infants and children aged 1≤12 years (10≤40 kg BW)	200-400 [b] mg/kg BW in 3-4 divided doses

[a] Sum of gestational and postnatal age

[b] The high-dose regimen may be considered for severe infections and or serious infections (such as meningitis), in particular when known or suspected to be caused by organisms with moderate susceptibility.

No dose recommendations can be made for children with renal impairment.

Method of administration

Fomicyt is intended for intravenous use.

The duration of infusion should be at least 15 minutes for the 2 g pack size, at least 30 minutes for the 4 g pack size and at least 60 minutes for the 8 g pack size.

As damaging effects can result from inadvertent intra-arterial administration of products not specifically recommended for intra-arterial therapy, it is essential to ensure that fosfomycin is only administered into veins.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Risk of selecting for resistance and the need for combination therapy

In vitro, fosfomycin has been found to rapidly select for resistant mutants. Also, the use of intravenous fosfomycin alone has been associated with selection of resistance in clinical studies. Whenever possible, it is recommended that fosfomycin is administered as part of a combination antibacterial drug regimen to reduce the risk of selecting for resistance.

Limitations of the clinical data

The clinical data to support the use of intravenous fosfomycin for treatment of some of the listed indications is limited by a lack of adequate randomised controlled trials. Furthermore, various dose regimens have been used and no single intravenous dose regimen has been strongly supported by clinical trial data. It is recommended that fosfomycin is selected to treat the listed indications only when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment (see sections 4.3 and 4.8). If such reactions occur, treatment with fosfomycin must be discontinued immediately and adequate emergency measures must be initiated.

Clostridioides difficile-associated diarrhea

Clostridioides difficile-associated colitis and pseudo-membranous colitis have been reported with fosfomycin and may range in severity from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of fosfomycin. Discontinuation of therapy with fosfomycin and the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Sodium and potassium levels and risk of sodium overload

Sodium and potassium levels should be monitored regularly in patients receiving fosfomycin, in particular during prolonged treatment. Given the high content of sodium (0.32 grams) per gram of fosfomycin, the risk of hypernatraemia and fluid overload should be assessed before starting treatment, especially in patients with a history of congestive heart failure or underlying comorbidities such as nephrotic syndrome, liver cirrhosis, hypertension, hyperaldosteronism, pulmonary oedema or hypoalbuminemia as well as in neonates under sodium restriction. A low-sodium diet is recommended during treatment. An increase in the infusion length and/or a reduction to the individual dose (with more frequent administration) could also be considered. Fosfomycin may decrease potassium levels in serum or plasma, therefore potassium supplementation should be always considered.

Haematological reactions (including agranulocytosis)

In patients receiving fosfomycin intravenously haematological reactions including neutropenia or agranulocytosis have occurred (see section 4.8). Therefore, the leukocyte count should be monitored at regular intervals and if such reactions occur, an adequate medical treatment should be initiated.

Renal impairment

In patients with impaired renal function, adjust the dosage according to the grade of renal insufficiency (see section 4.2).

Excipients

1 g fosfomycin (equivalent to 1.32 g disodium fosfomycin) contains 14 mmol (320 mg) sodium, equivalent to 16 % of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult. One bottle with 2 g of fosfomycin contains 28 mmol (640 mg) sodium, one bottle with 4 g fosfomycin contains 56 mmol (1280 mg) sodium and one bottle with 8 g of fosfomycin contains 111 mmol (2560 mg) sodium.

4.5 Interaction with other medicinal products and other forms of interactions

Specific concerns relating to INR imbalance:

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic therapy. The severity of the infection or inflammation, patient age and general state of health appear to be risk factors. Under these circumstances, it is difficult to determine to what extent the infection itself or its treatment play a role in the INR imbalance. However, certain classes of antibiotics are more involved, particularly: fluoroquinolones, macrolides, cyclins, cotrimoxazole, and certain cephalosporins.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no data from the use of intravenously administered fosfomycin in pregnant women. Fosfomycin crosses the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Fosfomycin should therefore not be prescribed to pregnant women unless the benefit outweighs the risk.

Breast-feeding:

After the administration of fosfomycin, low quantities were found in human milk. Only scarce information about fosfomycin use during breastfeeding is available, therefore this treatment is not recommended as first choice for a breastfeeding woman, especially if she is breastfeeding a premature or new-born baby. No specific risk for a breastfed child was demonstrated, however, as with any other antibiotics a potential risk of changes in infant bowel flora should be taken into consideration.

Fertility:

No data in humans are available. In male and female rats oral administration of fosfomycin up to 1000 mg/kg/day did not impair fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No specific studies have been performed but patients should be informed that confusion and asthenia have been reported. This may influence some patients' ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are erythematous skin eruption, ion disbalances (see section 4.4), injection site reactions, dysgeusia and gastrointestinal disturbances. Other important adverse reactions include anaphylactic shock, antibiotic associated colitis and decreases in white blood cell counts (see section 4.4).

Tabulated list of adverse reactions

Undesirable effects are listed by body system and frequency using the following convention:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Not known	Agranulocytosis (transient), leucopenia, thrombocytopenia, neutropenia
Immune system disorders	Very rare	Anaphylactic reactions including anaphylactic shock and hypersensitivity (see section 4.4)
Nervous system disorders	Common	Dysgeusia,
	Uncommon	Headache
Investigations	Common	Hypernatremia, hypokalemia* (see section 4.4)
Gastrointestinal disorders	Uncommon	Nausea, vomiting, diarrhea
	Not known	Antibiotic-associated colitis (see section 4.4)
Hepatobiliary disorders	Uncommon	Blood alkaline phosphatase increased (transient), Transaminases increased (ALAT, ASAT), gamma-GT increased
	Not known	Hepatitis
Skin and subcutaneous tissue disorders	Common	Erythematous eruption
	Uncommon	Rash

	Not known	Angioedema, pruritus, urticaria
General disorders and administration site conditions	Common	Injection site phlebitis
	Uncommon	Asthenia

* see section below (Description of selected adverse reactions)

Description of selected adverse reactions:

Hypokalaemia may result in diffuse symptoms such as weakness, tiredness or oedema and/or muscle twitching. Severe forms may cause hyporeflexia and cardiac arrhythmia. Hypernatraemia may be associated with thirst, hypertension and signs of fluid overload such as oedema (see section 4.4). Severe forms may cause confusion, hyperreflexia, seizures and coma.

Paediatric population

Limited safety information is available from the paediatric population. Frequency, type and severity of adverse reactions may be expected to be similar to the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://sideeffects.helath.gov.il

4.9 Overdose

Experience regarding the overdose of fosfomycin is limited. Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin. In the event of overdose, the patient must be monitored (particularly for plasma/serum electrolyte levels), and treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the active substance. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; Other antibacterials

ATC-Code: J01XX01

Mechanism of action

Fosfomycin exerts a bactericidal effect on proliferating pathogens by preventing the enzymatic synthesis of the bacterial cell wall. Fosfomycin inhibits the first stage of intracellular bacterial cell wall synthesis by blocking peptidoglycan synthesis.

Fosfomycin is actively transported into the bacterial cell via two different transport systems (the sn-glycerol-3-phosphate and hexose-6 transport systems).

Pharmacokinetic/pharmacodynamic relationship

Limited data indicate that fosfomycin most likely acts in a time-dependent manner.

Mechanism of resistance

Main mechanism of resistance is a chromosomal mutation causing an alteration of the bacterial fosfomycin transport systems. Further resistance mechanisms, which are plasmid- or transposon-borne, cause enzymatic inactivation of fosfomycin by binding the molecule to glutathione or by cleavage of the carbon-phosphorus-bond in the fosfomycin molecule, respectively.

Cross-resistance

Cross-resistance between fosfomycin and other antibiotic classes is not known.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for intravenous fosfomycin and are listed here:

https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Susceptibility

The prevalence of acquired resistance of individual species may vary geographically and over time. Local information about the resistance situation is therefore necessary, particularly in order to ensure appropriate treatment of severe infections.

The information below gives only approximate guidance on the probability as to whether the micro-organism will be susceptible to fosfomycin or not.

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus
Aerobic Gram-negative microorganisms
Citrobacter freundii
Citrobacter koseri
Escherichia coli
Haemophilus influenzae
Neisseria meningitidis
Salmonella enterica
Anaerobic microorganisms
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Species in which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus epidermidis
Streptococcus pneumoniae
Enterococcus spp.
Aerobic Gram-negative microorganisms
Enterobacter cloacae
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumonia
Proteus mirabilis
Pseudomonas aeruginosa

Serratia marcescens
Anaerobic Gram-positive microorganisms
Clostridium spp.
Inherently resistant species
Aerobic Gram-positive microorganisms
Staphylococcus saprophyticus
Streptococcus pyogenes
Aerobic Gram-negative microorganisms
Legionella pneumophila
Morganella morganii
Stenotrophomonas maltophilia
Anaerobic Gram-negative microorganisms
Bacteroides spp.
Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.

5.2 Pharmacokinetic properties

Pharmacokinetics

A single intravenous infusion of 4 g and 8 g of fosfomycin in young healthy males resulted in maximum serum concentrations (C_{max}) of approximately 200 and 400 micrograms/ml, respectively. The serum half-life was approximately 2 hours. In elderly and/or critically ill male and female subjects, single intravenous doses of 8 g of fosfomycin resulted in mean C_{max} and half-lives in plasma of approximately 350–380 micrograms/ml and 3.6–3.8 h, respectively.

Distribution

The apparent volume of distribution of fosfomycin is approximately 0.30 l/kg body weight. Fosfomycin is distributed well to tissues. High concentrations are reached in eyes, bones, wound secretions, musculature, cutis, subcutis, lungs and bile. In patients with inflamed meninges, cerebrospinal fluid concentrations reach approximately 20–50% of the corresponding serum levels. Fosfomycin passes the placental barrier. Low quantities were found in human milk (about 8 % of the serum concentrations). The plasma protein binding is negligible.

Metabolism

Fosfomycin is not metabolised by the liver and does not undergo enterohepatic circulation. No accumulation is therefore to be expected in patients with hepatic impairment.

Elimination

80–90% of the quantity of fosfomycin administered to healthy adults is eliminated renally within 12 hours after a single intravenous administration. A small amount of the antibiotic is found in faeces (0.075%). Fosfomycin is not metabolised, i.e. the biologically active compound is eliminated. In patients with normal or mildly to moderately impaired renal function (creatinine clearance ≥ 40 ml/min), approximately 50–60% of the overall dose is excreted within the first 3-4 hours.

Linearity

Fosfomycin shows linear pharmacokinetic behaviour after intravenous infusion of therapeutically used doses.

Special populations

Very limited data are available in special populations.

Elderly

No dose adjustment is necessary based on age alone. However, renal function should be assessed and the dose should be reduced if there is evidence of renal impairment (see section 4.2).

Paediatric population

The pharmacokinetics of fosfomycin in children and adolescents aged 3–15 years as well as in term newborns with normal renal function are generally similar to those of healthy adult subjects. However, in renally healthy neonates and infants up to 12 months, the glomerular filtration rate is physiologically decreased compared to older children and adults. This is associated with a prolongation of the elimination half-life of fosfomycin in dependence on the stage of renal maturation.

Renal insufficiency

In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal insufficiency. Patients with creatinine clearance values of 40 ml/min or less require dose adjustments (see also section 4.2. “Renal impairment” for further details).

In a study investigating 12 patients under CVVHF customary polyethylene sulfone haemofilters with a membrane surface of 1.2 m^2 and a mean ultrafiltration rate of 25 ml/min were employed. In this clinical setting, the mean values of plasma clearance and elimination half-life in plasma were 100 ml/min, and 12h, respectively.

Hepatic insufficiency

There is no requirement for dosage adjustments in patients with hepatic insufficiency since the pharmacokinetics of fosfomycin remains unaffected in this patient group.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.

No carcinogenicity data are available for fosfomycin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Succinic acid.

6.2 Incompatibilities

Although no chemical/pharmaceutical incompatibilities have been found, Fomicyt solutions should not be mixed together with other parenteral preparations with the exception of those listed in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, protected from light, unless preparation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30 °C.
For storage of the solution for infusion see section 6.3.

6.5 Nature and contents of container

Clear type-I glass bottles with a rubber stopper (bromobutyl rubber) and pull-off cap
Containing

- 2 g (in 30 ml bottle) in packs of 10 bottles each
- 4 g (in 30 ml bottle) in packs of 10 bottles each
- or 8 g (in 50 ml bottle) in packs of 10 bottles each.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation of the solution for infusion

FOMICYT must be reconstituted and diluted prior to administration.

Water for Injections and Glucose Infusion 50 mg/ml (5 %) or Glucose Infusion 100 mg/ml (10 %) may be used as solvent for the reconstitution and dilution. Sodium chloride containing solvents must not be used (see section 4.4).

Reconstitution

Shake the vial prior to the reconstitution to loosen up the powder. Reconstitute the 2 g or 4 g vials with 20 ml and the 8 g vial with 40 ml of solvent. Shake well to dissolve. A slight degree of warming occurs when the powder is dissolved.

Caution: This intermediate solution is not for direct infusion. Withdraw the solution completely from the original vial. Transfer the withdrawn solution into an infusion bag or other suitable infusion container for further dilution as follows.

Dilution

Transfer the reconstituted contents of **2 g vial**s into an infusion container with further **30 ml** of solvent.

Transfer the reconstituted contents of **4 g vials** into an infusion container with further **80 ml** of solvent.
Transfer the reconstituted contents of **8 g vials** into an infusion container with further **160 ml** of solvent.

The resulting solution for infusion is clear and colourless to slightly yellowish.

Displacement value

The displacement values for the solutions are 1 ml for the 2 g pack size, 2 ml for the 4 g pack size and 4 ml for the 8 g pack size.

These volumes are equivalent to an increase of volume of 2 %. This has to be considered when not the entire volume of the final diluted solution is used.

7. MANUFACTURER

InfectoPharm Arzneimittel und Consilium GmbH, Von-Humboldt-Str. 1, 64646 Heppenheim, Germany

8. REGISTRATION HOLDER

Tzamal Bio-Pharma, 20 Hamagshimim St.,Kiryat Matalon ,Petah-Tikva.

9. MARKETING AUTHORISATION NUMBERS

173-51-37318-99
173-52-37319-99
173-53-37320-99

Revised in March 2025.

Fom_SPC_TZ03.2025