Summary of Product Characteristics

1. Name of the Medicinal Product

A-Foscid

2. Quality and Quantitative Composition

Each vial contains Fosfomycin Sodium equivalent to Fosfomycin 2.0 g.

Each vial contains Fosfomycin Sodium equivalent to Fosfomycin 4.0 g.

3. Pharmaceutical Form

Powder for solution for infusion.

White to cream-colored sterile powder for injection.

4. Clinical Particulars

4.1 Therapeutic indication:

Fosfomycin is indicated for the treatment of the following infections in adults and children including neonates (see section 5.1):

- Osteomyelitis
- Complicated urinary tract infections
- Nosocomial lower respiratory tract infections
- Bacterial meningitis
- Bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Fosfomycin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of the infections listed above, or when these alternative antibacterial agents have failed to demonstrate efficacy.

For information regarding the combination with other antibiotics see section 4.4 and 4.5.

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 bases 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):

Fosfomycin is primarily excreted renally unchanged. The general dosage guidelines for adults with estimated creatinine clearance > 80 ml/min are as follows:

Indication	Daily dose
Osteomyelitis	12-24 g [a] in 2-3 divided doses
Complicated urinary tract infection	12-16 g [a] in 2-3 divided doses
Nosocomial lower respiratory tract infection	12-24 g [a] in 2-3 divided doses
Bacterial meningitis	16-24 g [a] in 3-4 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.

Dosage in renal insufficiency

The dose recommendations for patients with renal impairment are based on pharmacokinetic modelling and limited clinical data; safety and efficacy have not yet been evaluated in clinical trials.

It is unclear if dose reductions are necessary for patients with an estimated creatinine clearance between 40-80 ml/min. Great 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. In adults, creatinine clearance may be calculated according to the following formula be Cockroft and Gault:

$$\text{Creatinine clearance } (CL_{CR}) \text{ in men [ml/min]} = \frac{(140 - \text{age [years]} \times \text{body weight [kg]})}{72 \times \text{serum creatinine [mg/dl]}}$$

In order to calculate CL_{CR} in women, the result of this formula is multiplied by 0.85.

Dosage table for patients with impaired renal function:

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.

The first dose should be increased by 100% (loading dose), 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).

No clinical data exist for intravenous fosfomycin in patients undergoing pre-dilution CVVHF or other forms of renal replacement therapy.

Hepatic impairment

There are no data indicating that dose adjustment is necessary in patients with hepatic impairment.

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).

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):

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 and duration of administration

Method of administration

Fosfomycin is intended of intravenous administration. 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.

Use only clear solutions.

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

For preparation of the solution for infusion see section 6.6

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. Relevant therapeutic guidelines should be adhered to when deciding treatment duration.

4.3 Contraindication

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

4.4 Special warning and precautions for use

Consideration should be given to co-administering intravenous fosfomycin with another antibacterial agent, taking into account the remaining susceptibilities of the pathogen(s) under treatment. As it is unknown whether the development of antibacterials should also be considered in order to prevent the emergence of resistance.

A high sodium load associated with the use of fosfomycin may result in decreased levels of potassium in serum or plasma. A low-sodium diet is recommended during treatment. The substitution of potassium may be necessary in some cases. Serum electrolyte levels and water balance must be monitored during therapy. Caution is advised when fosfomycin is use in patients with cardiac insufficiency, hypertension, hyperaldosteronism, hypernatremia or pulmonary edema. During prolonged treatment with high doses, blood potassium levels should be monitored in particular in digitalized heart failure patients (possible hypokalaemia, see section 4.8).

Acute, potentially life-threatening hypersensitivity reactions (anaphylactic shock) may occur in very rare cases. At the first signs (including sweating, nausea, cyanosis), the infusion of fosfomycin must be immediately discontinued. The intravenous line should be left in place. Depending upon the clinical situation, appropriate emergency measures may need to be initiated.

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents including fosfomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patient who present with diarrhoea during or subsequent to the administration of fosfomycin.

Discontinuation of therapy with fosfomycin and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

In patients with severe renal insufficiency (creatinine clearance $\leq$ 40ml/min), the elimination of fosfomycin is substantially slowed. See section 4.2 for appropriate dosing of fosfomycin in renal insufficiency.

4.5 Interaction with other medicinal products and other forms of interactions

No drug-drug interaction studies have been performed with fosfomycin. To date, no clinically relevant pharmacological interactions between fosfomycin and other agents (drugs, stimulants or foodstuffs) have been reported.

4.6 Pregnancy and lactation

Pregnancy

For fosfomycin, no clinical data on pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Fosfomycin should therefore not be prescribed to pregnant women unless the benefit outweighs the risk.

Lactation

After the administration of fosfomycin, low quantities of fosfomycin were found in human milk. Fosfomycin should therefore not be administered during lactation, unless the benefit outweighs the risk.

4.7 Effects on ability to drive and use machine

Occasionally, even if the product is correctly administered, side effects may occur which impair the ability to drive and use machines (see also section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are gastrointestinal disturbances and injection site reactions. Other important adverse reactions include hypokalemia and/or hypernatremia.

Tabulated list of adverse reactions

Undesirable effects are listed by body system and frequency in accordance with the following classification:

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

System Organ Class	Frequency Category	Adverse Drug Reactions
Blood and lymphatic system disorders	Rare	Aplastic anemia, eosinophilia
	Frequency not known	Agranulocytosis, granulocytopenia, leucopenia, pancytopenia, thrombocytopenia, neutropenia
Immune system disorders	Very rare	Anaphylactic shock (see section 4.4)
Metabolism and nutrition disorders	Common	Hypernatremia and/or hypokalemia (see section 4.4)
	Uncommon	Decreased appetite, oedema
Psychiatric disorders	Frequency not known	Confusion
Nervous system disorders	Uncommon	Dysgeusia, headache
Eye disorders	Very rare	Visual impairment
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Frequency not known	Tachycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnea
	Frequency not known	Asthmatic attack
Gastrointestinal disorders	Common	Retching, stomach ache
	Uncommon	Nausea, vomiting, diarrhoea
	Frequency not known	Pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders	Uncommon	Blood alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase increased (transient)
	Very rare	Fatty liver (completely reversible after discontinuation of fosfomycin)
	Frequency not known	Hepatitis, cholestatic hepatitis, icterus, gamma-GT increase
Skin and subcutaneous tissue disorders	Common	Erythematous eruption
	Uncommon	Rash
	Frequency not known	Angioedema, facial oedema, pruritus, urticaria
General disorders and administration site conditions	Common	Injection site phlebitis
	Uncommon	Fatigue

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. Hypernatremia may be associated with hypertension and signs of fluid overload such as oedema (see section 4.4).

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.

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 drug. 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: antibiotics for systemic use, other antibacterials

ATC-Code: J01XX01

Mode 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 be 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 (PK)/pharmacodynamic (PD) relationship

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

Resistance mechanism

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

The mode of action of fosfomycin differs from that of all other antibiotic classes. Fosfomycin was generally found to be active *in-vitro* against clinical isolates of methicillin-resistant staphylococci, vancomycin-resistant enterococci, penicillin and erythromycin-resistant streptococci and multiresistant *Pseudomonas*.

Antimicrobial spectrum of fosfomycin (in vitro)

The data predict only the probability of micro-organism susceptibility to fosfomycin.

For intravenous fosfomycin, the susceptibility breakpoints established by the European Committee on Antimicrobial Susceptibility Testing are as follows (EUCAST breakpoint table version 5.0, 2015)

Species	Susceptible	resistant
Enterobacteriaceae	≤ 32 mg/l	> 32 mg/l
Staphylococcus spp.	≤ 32 mg/l	> 32 mg/l

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.

In-vitro activity spectrum of fosfomycin and resistance

The following table is based on the breakpoint according to EUCAST and comprises organisms relevant for the approved indications:

Commonly susceptible species
Aerobic Gram-positive microorganisms *Staphylococcus aureus* *Streptococcus pyogenes* *Streptococcus pneumoniae*
Aerobic Gram-negative microorganisms *Citrobacter* spp. *Edwardsiella* spp. *Enterobacter cancerogenus* *Escherichia coli* *Haemophilus influenzae* *Klebsiella oxytoca* *Neisseria* spp. *Proteus mirabilis* *Proteus penneri* *Providencia rettgeri*
Anaerobic microorganisms *Peptococcus* spp. *Peptostreptococcus* spp.
Species in which acquired resistance may be a problem
Gram-positive microorganisms *Enterococcus faecalis* *Staphylococcus epidermidis*
Gram-negative microorganisms *Enterobacter cloacae*

Klebsiella pneumonia *Proteus inconstans* *Pseudomonas aeruginosa* *Serratia marcescens*
Inherently resistant species
Gram-negative microorganisms *Morganella morganii*
Anaerobic microorganisms *Bacteroides* spp.

The physiologically important apathogenic anaerobic species, *Lactobacillus* and *Bifidobacterium*, are not susceptible to fosfomycin.

5.2 Pharmacokinetic properties

Pharmacokinetics

A single intravenous infusion of 4 g of fosfomycin in young healthy males resulted in maximum serum concentration (Cmax) of approx. 200 µg/ml. The serum half-life was approx. 2 hours.

Distribution

The apparent volume of distribution of fosfomycin is approx. 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 approx. 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 metabolized 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 10 hours after a single intravenous administration. Fosfomycin is not metabolized, i.e. the biologically active compound is eliminated. In patients with normal or mildly to moderately impaired renal function (creatinine clearance $\geq$ 40 ml/min), approximately 50-60% of the overall dose is excreted within the first 3-4 hours.

Linearity

Fosfomycin shows linear pharmacokinetic behavior 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 increase 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 “Dosage in renal insufficiency” 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

Subacute and chronic toxicity

The toxicity of fosfomycin following repeated administration for up to 6 months was evaluated in rats, dogs, rabbits and monkeys. At high intra-peritoneal doses of fosfomycin (> 500 mg/kg /day), rats developed respiratory arrest, tetanic cramps, anemia, a reduction of blood protein levels, increased serum cholesterol and reduced blood glucose. Furthermore, dogs and monkeys experienced diarrhea due to antibiotic-related changes in the intestinal flora following intravenous administration of doses of higher than 250 mg/kg /day and 500 mg/kg /day, respectively. In the rabbit, no toxicity was observed following intravenous administration of 400 mg/kg /day for a period of 1 month.

Reproductive toxicity

Fertility

In male and female rats, following repeated administration (via a pharyngeal tube) of up to 1400 mg/kg /day reduced fertility was observed at the maximum dose tested.

Teratogenicity

Fosfomycin was administered to mice, rats and rabbits via pharyngeal tube at maximum doses of 2 x 120 mg/kg /day, 1400 mg/kg /day and 420 mg/kg /day, respectively or intravenously to mice and rabbits at 55.3 mg/kg /day, and up to 250 mg/kg /day, respectively. There was no evidence of embryotoxicity or teratogenicity.

Perinatal and postnatal toxicity

In rats, a maximum dose of 2800 mg/kg /day was administered via a pharyngeal tube. There was no evidence of fetal or peri- and postnatal toxicity.

Mutagenicity

In-vitro tests were performed to test the alkylating capacity and the mutagenic effect of fosfomycin. Fosfomycin showed no alkylating effect. In the Ames test, no mutagenic effect was seen in test strains of *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537 and TA 1538, with and without addition of rat-liver homogenate) after exposure to fosfomycin at up to 1600 µg/ml.

6. Pharmaceutical Particulars

6.1 List of excipients: Succinic acid

6.2 Incompatibilities

Although no chemical/pharmaceutical incompatibilities have been found, A-Foscid solutions should not be mixed together with other parenteral preparations with the exception of those listed in section 6.3.

6.3 Shelf life

2 years

Chemical and physical in-use stability of the reconstituted and final diluted solution that has been produced under aseptic conditions has been demonstrated for 7 days at 25 ºC, 30 ºC and 40 ºC.

However, for a microbiological point of view, the product should be used immediately. Parenteral fosfomycin sodium should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit.

6.4 Special precautions for storage

Store below 30^{o} C

6.5 Nature and contents of container

Clear glass vial (Type I) closed with gray chlorobutyl rubber stopper and sealed with aluminium/polypropylene flip-off cap contains fosfomycin sodium eq. to fosfomycin 2 g and 4 g, packed or unpacked in a box of 1, 5, and 10 vials.

6.6 Special precautions for disposal and other handling

For single use only.

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

Preparation of the solution for infusion

Water for Injection, 5% Dextrose in water or 10% Dextrose in water and 0.9% Sodium chloride NSS may be used as solvent for the reconstitution and dilution has been demonstrated in-use stability report.

Caution: Sodium chloride containing solvent must not be used in some patients (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 of solvent. Shake well to dissolve. A slight degree of warning occurs when the powder is dissolved.

Caution: This intermediate solution is no for direct infusion. Withdraw the solution completely form 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 vials 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.

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

7. Marketing Authorization Holder

ABLE MEDICAL COMPANY LIMITED

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Mahasarakham 44160, Thailand

8. Marketing Authorization Numbers

xx xxxxx/yy

9. Date of authorization

DD/MMM/YYYY

10. Date of revision of the text

DD/MMM/YYYY